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ORIGINAL ARTICLES

THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

CLINICAL EXPERIENCE WITH 37 CASES

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IN 1943 Mackenzie and Mackenzie,[5] and Astwood and his associates[1] first reported in detail the striking effects of thiourea and related compounds upon the structure and function of the thyroid gland in lower animals. Since that time much additional experimental work with these substances in lower animals has been reported.[4] Thiourea and its related compound, 2-thiouracil, inhibit the synthesis of the thyroid hormone, probably by affecting an enzyme system in the gland which normally aids in the conversion of iodine into the completed hormone.[4] When the extrathyroidal thyroid hormone has been destroyed or excreted, a state of thyroid failure supervenes; this cannot be prevented or corrected by iodine, but can be counteracted by thyroxine. The thyroid gland becomes hyperplastic and enlarged, probably because of continued excessive stimulation by the thyrotropic hormone of the anterior pituitary. These characteristic effects cannot be produced in the absence of the pituitary.

The clinical use of thiouracil was first reported by Astwood in 1943,[2] and a number of additional clinical reports have appeared subsequently.[3,8,11] The normal human thyroid appears to be resistant to thiouracil and its function seems to be affected, if at all, only after prolonged administration. The drug exerts a marked effect upon the toxic human thyroid gland. Within 1 to 3 weeks after the daily oral ingestion of 0.2 to 1 gm. of thiouracil is begun, most of the manifestations of the disease begin to diminish. There is a decline in the basal metabolic rate and the heart rate, gain in weight, and general subjective improvement. The thyroid enlargement does not always subside, and may actually increase for a time; exophthalmos seldom

recedes.* A rise in the total serum cholesterol often occurs. The development of positive nitrogen, calcium and phosphorus balances has been reported.[9] Thiouracil has been employed both as a preoperative agent and in the prolonged treatment of thyrotoxicosis. It is partially destroyed in the intestinal tract and is excreted entirely in the urine. A number of toxic effects have been reported; these include neutropenia, various dermatoses, thrombocytopenia with purpura, jaundice, pharyngitis, myalgia, hematuria, diarrhea, chills and fever.[3,6,11]

TABLE 1.—COLOR, AGE, SEX, DISTRIBUTION

Color—						
White						33
Negro						4
Age in decades	2	3	4	5	6	7
	1	10	8	6	4	3
Sex distribution—						
Male						6
Female						31

TABLE 2.—TYPE OF GOITER, PREVIOUS THERAPY AND DURATION OF SYMPTOMS

Type of goiter—	
Nodular	2
Diffuse	29
Recurrent postoperative	5
Unclassified	1
Previous therapy—	
Iodine alone	4
Iodine and Roentgen ray	5
Thyroidectomy	5
Duration of symptoms—	
Under 6 months	17
Over 6 months	20

TABLE 3.—COMPLICATIONS OF THYROTOXICOSIS

Auricular fibrillation	4
Congestive heart failure	2
Ophthalmopathy	1
Myasthenia gravis	1
Psychoneurosis	1
Mitral stenosis and pregnancy	1
Diabetes mellitus and rheumatic heart disease	1

Material. This report describes our clinical experiences with 37 thyrotoxic patients treated with 2-thiouracil. We have been especially interested in the effects of such therapy when continued over protracted periods of time. In addition we have had the opportunity of examining necropsy material from a thyrotoxic patient who was prepared for thyroidectomy with thiouracil. Our observations also include ballistocardiographic data obtained in 9 thyrotoxic patients before, and at varying periods after thiouracil was begun. In Tables 1, 2 and 3 are presented clinical data pertaining to the patients receiving treatment. We have included in this group 1 patient whose treatment had to be stopped before its effect could be evaluated; she is included because she showed a marked neutropenic reaction associated with fever

* Astwood (Thiouracil Treatment in Hyperthyroidism, J. Clin. Endocrinol., **4**, 229, 1944) has recently reported that thiouracil therapy is often followed by apparent regression of exophthalmos, but our observations do not support this view.

and pharyngitis (*vide infra*). With one possible exception, Case 8 below, all of our patients presented unquestionable evidence of thyrotoxicosis. The initial basal metabolic rate was +20% or more in all except 1 patient, a woman who developed recurrent thyrotoxicosis following the removal of a large intrathoracic goiter. Her basal metabolic rate was only +12% before the institution of thiouracil therapy; but in other respects she presented the typical picture of thyrotoxicosis. Among the 30 patients with diffuse toxic goiter the enlargement was marked and firm in 3. The others presented moderate or slight diffuse goiter. With respect to the duration of symptoms our patients have arbitrarily been divided into two groups, depending upon whether their symptoms had been noted for more or less than 6 months. Evaluation of duration of symptoms in thyrotoxicosis is often difficult since the disease is frequently insidious in onset, and even severely toxic patients occasionally deny consciousness of all symptoms. Of the 5 patients showing recurrent postoperative thyrotoxicosis, 4 had previously been operated upon for toxic diffuse goiter; 1 had had a right hemithyroidectomy for a large nodular intrathoracic goiter.

TABLE 4.—RESPONSE TO TREATMENT

General response to treatment—	
Complete response	30
Partial response	4
Failures	2
Unclassified	1
Relapsing after withdrawal of thiouracil	10
Relapsing when dosage was reduced	3
Sustained remission when drug stopped	8
Sustained remission when drug reduced	3
Specific response—	
Rise in cholesterol	17
Effect on exophthalmos:	
Reduced	4
Increased	2
No change	11
Effect on goiter:	
Reduced	4
Increased	5
No change	27

Results of Treatment. In Table 4 are presented data pertaining to the effects of thiouracil therapy in our patients. It will be seen that 30 (81%) of the patients showed a definitely favorable response to thiouracil, which was reflected by a progressive fall in the basal metabolic rate to normal levels or below, usually associated with concomitant decline in heart rate, gain in weight and general subjective improvement. Four patients (10.9%) showed partial, but not completely satisfactory, improvement; 2 patients (5.4%) failed completely to respond to the drug. In 1 case, referred to above, thiouracil therapy had to be stopped before its results could be evaluated. Among the 30 patients showing a favorable response, 11 remained ambulatory throughout their treatment; the remainder were hospitalized for periods varying from 1 to 3 weeks at the beginning of treatment. The basal metabolic rate was determined at weekly intervals until normal levels were attained, and thereafter at intervals of 2 to 4 weeks. The time required for the basal metabolic rate to fall to +15% or below varied from 5 days to 34 weeks, the average being about 2 weeks. In 6 patients whose initial basal metabolic rates were +50% or higher, the average duration of thiouracil therapy before

the basal metabolic rate fell to +15% or below was 3+ weeks. Five of these patients were hospitalized during the early part of their treatment. The average period of therapy required to bring about a fall in the basal metabolic rate to +15% or below in 22 patients whose basal metabolic rates were below +50% was 2½ weeks. Of these patients 12 were hospitalized during the early part of treatment. Subjective improvement became manifest in from 1 to 12 weeks in the entire group, the average time being 2½ weeks. Three patients who had responded favorably showed definite evidence of relapse when the daily dose of thiouracil was reduced to 0.2 gm. or less, and 10 patients relapsed when the drug was completely withdrawn. Evidence of relapse appeared in from 1 to 4 weeks in these cases and was manifested by a rise in the basal metabolic rate and heart rate, as well as by recurrence of subjective phenomena. All patients who relapsed, however promptly responded when thiouracil was again given in daily doses of 0.4 to 1 gm. Three of these 10 patients have subsequently remained well for periods varying from 1 to 4 months following the complete withdrawal of thiouracil. One patient relapsed on 3 separate occasions when the drug was stopped, responding each time to renewed therapy. She finally elected thyroidectomy and was operated upon, following preoperative iodization, with a good result. Three patients have remained in remission for periods of time varying from 2 to 3 months upon daily doses of thiouracil of from 0.1 to 0.2 gm. Eight patients have remained in remission from 3 weeks to 7 months after complete withdrawal of therapy. Data pertaining to the duration of observation and dosage of thiouracil in 24 cases are shown in Figure 1.

In most cases thiouracil was given in doses of 0.6 gm. daily, in 3 divided doses, for 3 or 4 days. If no untoward reaction appeared the daily dose was then increased to 0.8 or 1 gm., given in 4 or 5 doses. A maximum daily dose of 1 gm. was then maintained until definite evidence of remission appeared, or until it became apparent that no favorable response could be expected. A maximum daily dose of 2 gm. was employed in 2 cases. When a complete remission was indicated by persistence of normal basal metabolic rate and heart rate for about 1 week, the daily dose was gradually reduced to 0.2 or 0.1 gm. When evidence of remission continued for 1 month on this dosage, the drug was usually withdrawn in an effort to determine whether the patient would remain well without medication. Adjuvant treatment consisted of phenobarbital or other sedatives, and various mixed vitamins. One patient, described below, also received irradiation to the pituitary and estrogenic substance by mouth in an effort to inhibit anterior pituitary activity.

In 10 patients estimates of the cardiac output per minute were made, using the ballistocardiographic method of Starr.[10] These determinations were made before treatment and were repeated at periods varying from 12 to 30 days after therapy was begun. In Table 5 are shown percentile changes in cardiac output in 9 of these patients, with percentile changes in their basal metabolic rates determined at

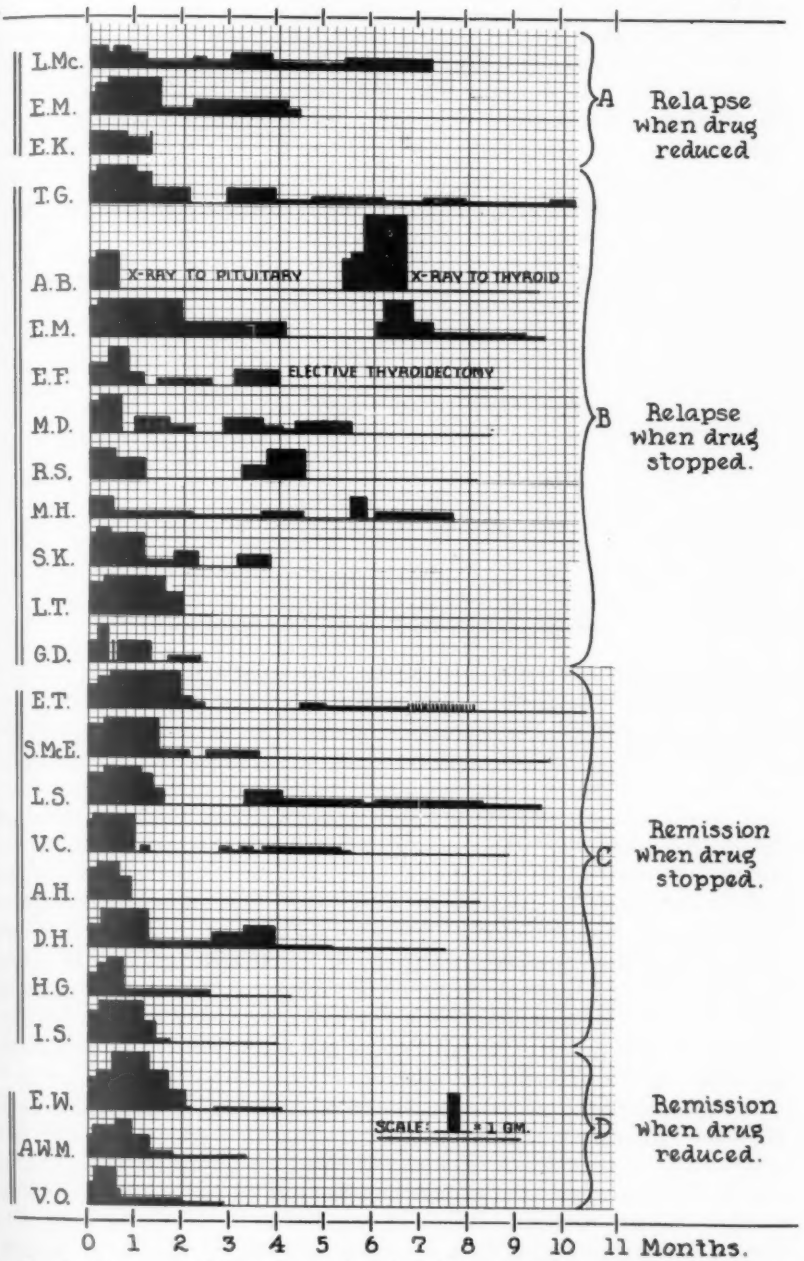


FIG. 1.—Dosage of thiouracil and duration of observation in 24 thyrotoxic patients: *A*, Cases showing relapse when dose was reduced; *B*, cases showing relapse when drug was stopped; *C*, cases showing remission when drug was stopped; *D*, cases showing remission when dose was reduced.

similar time intervals. In 1 patient, aged 13, cardiac output could not be calculated because of lack of normal standards for comparison, although the tracings indicated a reduction in the degree of hyperkinemia. It will be seen that the cardiac output was reduced in 8 patients coincidentally with the fall in basal metabolism which occurred during treatment. One patient (C. K.), who showed a normal cardiac output but an increased basal metabolism before treatment, had received iodine for several months until 3 weeks before institution of thiouracil therapy.

TABLE 5.—COMPARISON OF CHANGES IN BASAL METABOLISM WITH CHANGES IN CARDIAC OUTPUT, MEASURED BY BALLISTOCARDIOGRAM IN 9 PATIENTS DURING TREATMENT

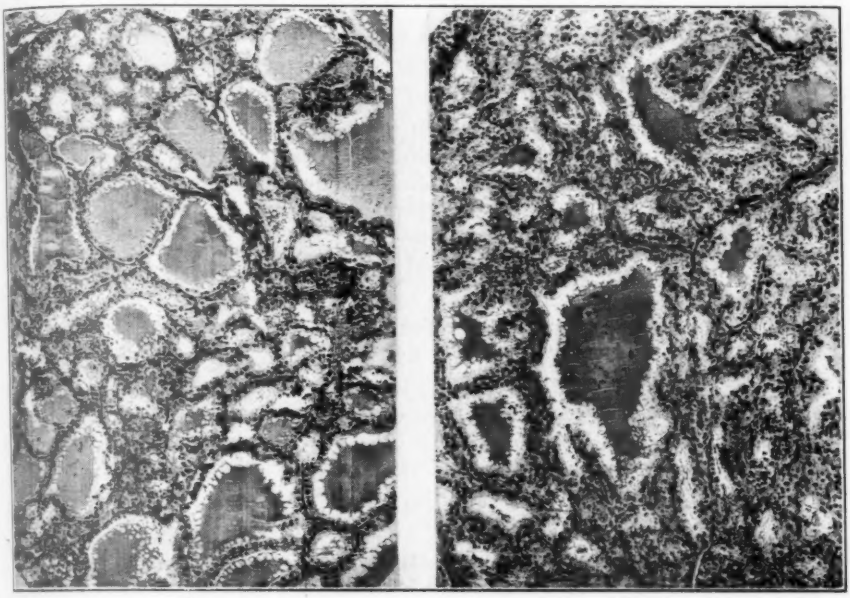
Patient	Percentile change in B.M.R.	Percentile change in cardiac output	Time interval in days
1. D. M.	−17	−21	30
2. C. K.*	−25	−23	17
3. V. McC.†	−10	−23	23
4. V. O.	− 8	−26	17
5. W. B.	−42	−86	26
6. J. M.	−34	+ 3	19
7. E. W.	−17	−44	28
8. H. C.	−37	−42	14
9. P. N.	−43	−30	15

* Cardiac output within normal limits prior to treatment.
† Received thiouracil 14 of the 23 days.

Thiouracil as a Preoperative Agent. Although our chief interest is centered upon the results of protracted therapy with thiouracil, we have employed it as a substitute for iodine in the preparation of 4 thyrotoxic patients for subtotal thyroidectomy. Three of these patients had diffuse toxic goiters and 1 had a toxic nodular goiter which had precipitated congestive heart failure. One patient, discussed below, died 20 hours after operation, but we do not believe that thiouracil contributed to his death. The other 3 patients responded satisfactorily to the preoperative use of the drug, and their postoperative courses were uneventful. In these patients the period of hospitalization from the beginning of thiouracil therapy to the time of operation was 17, 21 and 38 days, respectively. Their basal metabolic rates fell to +15% or below in 8, 14 and 31 days, respectively, after treatment was begun. One of these patients had taken iodine for 4 months before entering the hospital.

At operation the gross appearance of the thyroid glands in these patients differed markedly from that seen in patients treated preoperatively with iodine. There had been no apparent reduction in size of the goiter, and the glands were friable, vascular and bled rather freely. Histologic examination of the tissue in the 3 patients with toxic diffuse goiter showed a complete absence of the usual changes produced by iodine. Instead of the increase in colloid content and flattening of the acinar epithelium, there was marked, persistent hyperplasia, and the appearance was quite similar to that of the untreated toxic thyroid. The nodular goiter removed from the 4th patient presented no histologic evidence of toxicity, and contained

normal amounts of colloid, although the patient was clinically thyrotoxic. In 1 case a biopsy of the thyroid was taken before thiouracil was begun. Comparison of the histologic appearance of this tissue with that removed at operation (Fig. 2) shows the persistence of the typical thyrotoxic changes.



A *B*

FIG. 2.—Histologic appearance of toxic thyroid of patient V. McC. *A*, Before treatment (biopsy); *B*, after 23 days on thiouracil (thyroidectomy).

Three patients who had received thiouracil were subsequently operated upon following iodization, at intervals of 5, 6 and 7½ weeks after the withdrawal of thiouracil. Two of these patients failed to show a marked preoperative response to iodine, although their postoperative courses were not unusual. Sections from the thyroids of 2 of these patients showed some evidence of involution, although the colloid was somewhat thinner than usual and showed peripheral vacuolization. The thyroid of the third patient, which was markedly and diffusely enlarged, showed advanced involution with large amounts of colloid, despite the fact that he was severely toxic and resistant to both thiouracil and iodine.

Complications of Treatment. Untoward reactions attributed to thiouracil were observed in 8 patients.* The most important complication was that of severe leukopenia, associated with pharyngitis and fever, which was observed in 2 cases. The first patient was a white woman aged 41 years. Her leukocyte count dropped to 1200 per

* One of these patients who exhibited urticaria has not been included in our series because the diagnosis of thyrotoxicosis was doubtful.

c.mm. (28% neutrophils) after receiving thiouracil for 23 days. Two days later the leukocyte count was 1850 per c.mm. (12% neutrophils), her temperature had risen to 104° F. and there was severe acute tonsillitis and pharyngitis. No localized ulcerative or necrotic lesions appeared in the mouth or pharynx. Thiouracil was stopped when the leukopenia was first noted, and pentose nucleotide injections were started when the fever appeared. The pharyngitis and fever subsided in 3 days and the leukocyte count returned to 3800 per c.mm. (30% neutrophils) on the 5th day. Eight days later thiouracil was again given in doses of 0.2 gm. daily, but after 6 days the leukocyte count again fell to 2400 per c.mm. and the drug was again stopped, although other symptoms did not reappear. After an interval of 1 month thiouracil was again started cautiously in doses of 0.2 gm. daily, and no subsequent fall in leukocyte count occurred, although treatment was continued for 2 months. The thyrotoxic phenomena then subsided and the patient has remained well for 3 months without medication.

The second patient was a white man, aged 22 years. After receiving thiouracil in doses of 0.6 to 1 gm. daily for 9 days, pharyngitis, chills and fever appeared with a leukocyte count of 2200 per c.mm. (69% neutrophils). The drug was stopped and her signs and symptoms disappeared within 3 days. After 33 days thiouracil was resumed. After taking 0.4 gm. in divided doses, fever (100.4° F.), cervical adenitis and slight pharyngitis appeared, although the leukocyte count remained normal. This patient gave a history of allergy, and had developed a dermatosis following iodine therapy 6 years previously.

In addition, 14 other patients whose leukocyte counts were within normal limits prior to the institution of thiouracil therapy, showed a fall in total leukocyte count below 5000 per c.mm. within 4 to 55 days after the drug was begun. In 6 of these patients, the leukocyte count returned to normal levels despite continuation of therapy. One patient whose count fell from 8200 to 4100 per c.mm. after 10 days on thiouracil, showed a normal leukocyte count on the following day. Normal leukocyte levels were maintained thereafter while the daily dosage of thiouracil remained at 1 gm. for 7 months. At the end of that time the leukocyte count had again fallen to 2800 per c.mm. with a normal differential formula. Splenomegaly and moderate generalized adenopathy were found before treatment was begun; the splenomegaly later disappeared. Aspirated sternal bone marrow examined at the time leukopenia first appeared was normal.

Two patients developed mild maculopapular facial eruptions 11 and 19 days respectively after beginning treatment. Two patients, both of whom gave histories strongly suggestive of allergy, complained of urticaria after 7 and 8 days respectively on the drug.* One of these patients showed slight edema of the ankles and a plasma chloride concentration of 106 milliequivalents per liter after taking thiouracil for 1 month. Mild pharyngitis and fever, probably attributable to

* One of these patients who exhibited urticaria has not been included in our series because the diagnosis of thyrotoxicosis was doubtful.

thiouracil, appeared in 1 patient after 10 days of treatment. One patient complained of myalgia and anorexia 48 hours after the institution of treatment, and showed a regular evening rise in temperature to 101° F. which continued until thiouracil was stopped after 2 weeks. Despite these reactions, her basal metabolic rate fell to normal, and auricular fibrillation, which had previously been present, disappeared. One patient, who had previously taken the drug for 43 days without untoward effect, developed severe pruritus 21 days after resumption of thiouracil.

Comment on Selected Cases. Examination of the patients who failed to respond satisfactorily to thiouracil does not show any significant common factor or pattern. The following patients showed only a partial response to treatment.

Case Reports. CASE 1. J. B., an unmarried white girl, age 19, had thyrotoxic symptoms for about 3 months. Nervousness and tachycardia were prominent. There was moderate exophthalmos, but the thyroid gland was only slightly enlarged. The basal metabolic rate was +62%. The patient was kept at rest in the hospital for 17 days and thiouracil was given in daily doses of 0.6 to 1 gm. for 27 days. The basal metabolic rate fell to +24% after 14 days of treatment, but had risen again to +41% after 27 days of treatment. During this time the serum cholesterol rose from 179 to 291 mg. per 100 cc. Subjective improvement was slight, and she gained only 3 pounds. Thiouracil was withdrawn after 27 days and thyroid irradiation was begun. A marked aggravation of symptoms followed the institution of irradiation and this treatment was stopped after 1 week. Twenty-six days later, preoperative iodization was begun. After 13 days of iodine therapy her basal metabolic rate was still +38%. Subtotal thyroidectomy was performed at this time. Three months after operation she had gained 20 pounds but still showed a moderate tachycardia and her blood pressure was 140/100. Her menses had stopped and growth of hair on the lower abdomen was noted. The hypertension, amenorrhea and beginning hirsutism suggest the possibility that her thyrotoxicosis may have been an early episode in the development of Cushing's disease.

CASE 2. A. B., a white male, age 47, was first seen 2 months after the explosive onset of severe hyperthyroidism with very slight enlargement of the thyroid gland. The basal metabolic rate was +48%, there was severe ophthalmopathy with edema of the lids and conjunctivæ, superficial corneal erosion, occasional diplopia and an exophthalmometer reading of 28 mm. in each eye. In addition to thiouracil the patient was kept at bed rest in the hospital, receiving a high caloric diet with extra vitamins, sedation and estrogenic substance by mouth. He also received a total of 2000 r units of irradiation to the pituitary area. There was gradual but steady improvement; after 43 days on thiouracil his basal metabolic rate had fallen to +7%, the heart rate was 76 and he had gained 7 pounds. All the ocular phenomena except the exophthalmos gradually disappeared. He remained well with steadily increasing weight for 3½ months, at the end of which time he was allowed to return to work. Two weeks later his basal metabolic rate had risen to +28% and tachycardia, palpitation and nervousness recurred. Thiouracil was resumed in dosage up to 2 gm. daily, but after 3 weeks of such therapy his basal metabolic rate was +30% and his pulse rate was 132 per minute. The exophthalmos persisted, but the other ocular phenomena did not recur. At this time severe generalized pruritus appeared and thiouracil was stopped. Thyroidectomy has been avoided because of the severe ophthalmopathy. The patient has subsequently received intermittent iodization alternating with thyroid irradiation. At the time of writing he is still moderately thyrotoxic with a basal metabolic rate of +19%.

CASE 3. R. S., a white married woman, age 35, when first seen was about 4 months pregnant. Enlargement of the thyroid had been noted since the age of 9, but had increased markedly during her pregnancy. Although she denied symptoms, there was evidence of definite thyrotoxicosis. The thyroid gland was markedly and diffusely enlarged and the basal metabolic rate was +27%. Her resting pulse rate was 110 per minute. There was a presystolic apical murmur and the cardiac contour in the orthodiagram suggested mitral stenosis. The patient was kept at bed rest in the hospital for 15 days, during which time thiouracil was given in doses of 0.8 to 1 gm. daily. After 29 days her basal metabolic rate had fallen to −1 per cent and thiouracil was withdrawn. One month later the basal metabolic rate had again risen to +27% and thiouracil was again begun in dosage of 0.4 gm. daily. At this time the administration of iodine (10 mg. daily) was also instituted in order to insure an adequate supply of iodine for the fetus. Although thiouracil was continued in daily doses of from 0.4 to 0.8 gm. for the next 8 weeks, the patient's basal metabolic rate varied from +32 to +45%, the thyroid increased further in size and intermittent tachycardia persisted. Thiouracil was stopped 1 week before delivery and Lugol's solution was given in daily doses of 2 cc. The patient was delivered at term, without difficulty, of a healthy male infant which showed no evidence of thyroid enlargement or dysfunction. Seven weeks after delivery and 8 weeks after withdrawal of thiouracil her basal metabolic rate was +37%, the thyroid enlargement had increased further and the patient still appeared markedly thyrotoxic. Thyroidectomy was advised but not accepted. It is quite possible that this patient's pregnancy may have prevented a more complete response to thiouracil.

CASE 4. W. B., a white male, age 68, had been nervous, with tachycardia and intermittent abdominal pain, for 7 months, during which time he had lost 60 pounds. A diagnosis of gastric ulcer was made in another hospital after two periods of treatment and study, including Roentgen ray examination. Two months before admission he had received iodine for a period of 2 weeks. Examination showed marked weight loss and tachycardia with a tremendous increase in cardiac output (+234%). The thyroid was only slightly enlarged. The basal metabolic rate was +72%. There was no Roentgen evidence of peptic ulcer. The basal metabolic rate fell to +30% after the patient had received 1 gm. thiouracil daily for 2 weeks. After 1 month of such treatment, during which time he was hospitalized and given a high calorie diet with supplementary vitamins and sedatives, his basal metabolic rate was still +31% and his tachycardia had not materially decreased. However, he had gained 11 pounds, was subjectively much improved and his cardiac output had fallen to +128%.

The following 2 cases failed completely to respond.

CASE 5. W. L., a white male, age 29, had had thyrotoxic symptoms for 10 months prior to admission, with loss of 50 pounds. He had received large doses of iodine for 2½ months before we saw him. On admission to the hospital he presented a classical picture of extremely severe thyrotoxicosis, showing marked weight loss, sweating, tremor, muscular weakness, exophthalmos and a very large diffuse firm goiter. The basal metabolic rate was +75%. He received thiouracil in daily dosage of 0.6 to 0.8 gm. for 23 days without evidence of sustained improvement. The basal metabolic rate fell to +48% on the 14th day of treatment, but on the 23rd day had again risen to +73%. During this time he lost 7 pounds, and his tachycardia did not subside. After the withdrawal of thiouracil he was again given iodine, and a right hemithyroidectomy was successfully performed 16 days later. Two months later a left hemithyroidectomy was performed after another period of iodine therapy, with eventual complete relief of the thyrotoxicosis. This patient was the first in our series to receive thiouracil (June, 1943) and we did not at the time appreciate the effect of previous iodization upon the response of the toxic thyroid to thiouracil. It is possible that a more prolonged period of therapy with the latter drug might have produced more satisfactory results.

XUM

CASE 6. M. H., a white female, age 26, had had symptoms of thyrotoxicosis for about 8 months. She had received iodine for two periods of 8 and 3 weeks respectively during the 7 months prior to admission to the hospital. There was slight diffuse thyroid enlargement and moderate exophthalmos, and her initial basal metabolic rate was +33%. She also presented definite evidence of myasthenia gravis, which was confirmed by her response to prostigmine. She received thiouracil in daily dosage of 0.6 to 1 gm. for 40 days without favorable subjective or objective response. During this period she lost 3 pounds. Her basal metabolic rate rose to +44% after 12 days of treatment, fell to +14% on the 32nd day and rose again to +22% on the 40th day. On the 2nd day of treatment she developed a diffuse respiratory infection with fever up to 102° F. and received sulfadiazine for 2 days. Irradiation therapy to the thyroid and thymus areas was begun 25 days after the withdrawal of thiouracil. The thyrotoxic manifestations have almost completely disappeared after two series of irradiation and there has been concomitant improvement in her myasthenia, although she still requires prostigmine and ephedrine. This patient has been consistently unable to coöperate satisfactorily in her basal metabolism determinations and all of the values obtained are open to question. There can be no doubt, however, as to the existence of both the thyrotoxicosis and myasthenia gravis. Her improvement following irradiation therapy is likewise beyond question.

The following cases are described briefly because of some features of unusual interest.

CASE 7. A. S., a colored male, age 48, had had thyrotoxic symptoms for 16 months, with a 30 pound weight loss. Examination showed exophthalmos with stare, emaciation, muscular weakness with marked tremor, diffuse nodular goiter of moderate degree, auricular fibrillation, generalized adenopathy and slight enlargement of the spleen. The basal metabolic rate was +62%; there was a slight lymphocytosis (leukocytes 8200 per c.mm. with 54% lymphocytes). After 22 days on thiouracil, during which time he also received digitalis, a high caloric diet and extra vitamin B with continuous bed rest in the hospital, he showed little evidence of improvement. Auricular fibrillation was still present, he had lost 2 pounds, and his basal metabolic rate was +31%. Subtotal thyroidectomy was advised, but was refused. The patient requested that he be allowed to continue thiouracil while resuming his work as a cement finisher, and this request was somewhat reluctantly granted. Two weeks after discharge from the hospital, on a daily dose of 0.6 gm. of thiouracil, his basal metabolic rate was +55% and auricular fibrillation persisted, but he had gained 14 pounds with no evidence of congestive heart failure and felt much better. Six weeks later his basal metabolic rate was +26%, he had gained another 7 pounds, the cardiac rate was 90 per minute and the rhythm was regular. The spleen was still palpable but the adenopathy was less marked. The daily dose of thiouracil was increased from 0.6 to 0.8 gm. Except for one 10-day period the patient took thiouracil for 6 months continuously after leaving the hospital. At the end of that time he had gained 28 pounds, the cardiac rate and rhythm were normal, splenomegaly had disappeared, the goiter was somewhat smaller and his basal metabolic rate was +5%. His eyes, however, had increased 1 mm. in prominence and the leukocyte count had fallen to 2800 per c.mm. with a normal differential formula. Thiouracil was then stopped because of the leukopenia and the disappearance of the thyrotoxic phenomena. This case illustrates the occasional necessity for prolonged therapy with thiouracil before satisfactory response is obtained, as well as the fact that leukopenia may appear or reappear after the prolonged administration of thiouracil.

CASE 8. E. M., a white female, age 50, had had several attacks of rheumatic fever in childhood, and heart disease had been diagnosed at the age of 20. She had been under medical treatment for recurrent congestive heart failure for 2 years prior to admission. Following the death of her husband

9 months before admission, she had become increasingly weak and dyspneic and had lost about 40 pounds. Examination showed marked nervousness, tremor, slight stare, auricular fibrillation, signs of congestive heart failure, and evidence of mitral stenosis and regurgitation with probable tricuspid regurgitation. There was no thyroid enlargement. The basal metabolic rate was +47%. Her response to digitalis and other measures directed toward relieving the circulatory failure was unsatisfactory, and the ventricular rate remained rapid. She likewise failed to improve after the administration of potassium iodide for 1 month. At this time, when her basal metabolic rate was +34%, the potassium iodide was replaced by thiouracil in dosage of 1 gm. daily. After 12 days the basal metabolic rate was +15% and the congestive phenomena had markedly improved; although she continued in auricular fibrillation the ventricular rate had fallen to approximately 90 per minute. She continued her medication at home for 2 weeks after which she returned to the hospital. At this time, after 6 weeks of thiouracil therapy, her basal metabolic rate was +11% and remained at that level until her discharge 2 weeks later. During this time she received Cedilanid (2 mg. daily) and 2 cc. of a mercurial diuretic by intravenous injection 3 times weekly. She remained in auricular fibrillation, but the ventricular rate remained between 80 and 90 per minute and she presented no evidence of congestive heart failure except a firm enlargement of the liver (cardiac cirrhosis). There was marked improvement in her nervousness. Thyroidectomy was advised but not accepted.

The diagnosis of thyrotoxicosis could not be made with certainty in this case, as the initial high basal metabolic rate might have resulted from her congestive heart failure. However, thyrotoxicosis was strongly suggested by the history of weight loss, the stare, nervousness and refractoriness to digitalis. Her marked improvement and the concomitant decline in basal metabolism following thiouracil likewise suggest a thyrotoxic factor. If it be assumed that thyrotoxicosis was not present, her apparent response to thiouracil still remains of interest, since in this event it would suggest that some antithyroid action of the drug upon a normally functioning gland may have been a factor contributing to her recovery from congestive heart failure (see Comment).

CASE 9.—V. McC., a white male, age 27, had first had thyrotoxic symptoms at the age of 24. A partial thyroidectomy was performed soon afterwards in another hospital which he left, against advice, 3 days after operation. His symptoms persisted with progressive weight loss of 74 pounds until his admission to our hospital 3 years later. At that time he was severely emaciated with marked muscular weakness and tremor, exophthalmos and a nodular goiter. The basal metabolic rate was +38%. He had taken iodine for 3 weeks prior to admission. A preoperative biopsy of the thyroid was taken, but the patient left the hospital against advice before thiouracil could be started. He was readmitted 11 days later, having taken iodine for several days during the interval. After taking thiouracil in doses of 1 gm. daily for 16 days, his basal metabolism was +28%, but he had gained 15 pounds, his pulse rate had declined, and he was anxious for operation. His preoperative course was marked by several episodes of morning vomiting which were inexplicable at the time but which in the light of later knowledge seemed due to alcoholism. After 16 days of thiouracil therapy, a subtotal thyroidectomy was performed. The patient took the anesthesia badly, became cyanotic and went into shock on the table after losing a rather large amount of blood. The thyroid gland was much larger than it had seemed on palpation. It was extremely vascular and friable. Bleeding was very free and difficult to control. Despite several transfusions of blood and plasma, the patient remained in serious condition and did not react from the anesthesia. He died 20 hours after operation, presenting the picture of combined shock, anoxia and thyrotoxic crisis.

Necropsy showed bilateral bronchopneumonia with a histologic appearance which suggested that it had been present for about 3 days. Sections of the thyroid (see Fig. 2) presented an appearance quite unlike that of the iodized

toxic thyroid or the untreated toxic gland and resembled that described by Williams and Clute[11] in the toxic thyroids of patients treated with thiocuracil. There was hypertrophy and hyperplasia of the epithelial acinar cells with marked reduction in colloid content of the acini and there was an increase in the vascularity of the gland with marked congestion. The pituitary, parathyroids and testes were normal. There was congestion in the spleen and kidneys and the liver showed slight fatty dystrophy.

It seems unlikely that thiouracil was a factor in this unfortunate fatality. In retrospect, it is obvious that we should not have permitted the patient to undergo thyroidectomy and that the operation, once begun, should have been discontinued when he reacted badly to the anesthetic. The pathologic report of a 3 day old bronchopneumonia is difficult to understand as the patient presented neither fever, leukocytosis, nor any sign or symptom suggesting such a process. It was later discovered that the patient had been in the habit of consuming much more alcohol than was realized at the time of his admission.

Case 10.—V. M., a 13 year old girl, developed symptoms of thyrotoxicosis about 1 month before admission to the hospital. She had suffered several attacks of rheumatic fever beginning at the age of 6. Between the ages of 7 and 11 she had several epileptiform seizures. Glycosuria was discovered at the age of 12 and she had received 20 units of protamine zinc insulin and 10 units of unmodified insulin daily since that time. Examination showed slight exophthalmos, a moderate, diffuse thyroid enlargement, tachycardia, tremor, and a loud apical systolic murmur. The basal metabolic rate was +27% and the fasting blood sugar was 102 mg. per 100 cc. After receiving thiouracil in daily doses of 0.6 to 1 gm. for 10 days, her basal metabolic rate had fallen to +3% and her thyrotoxic symptoms were well controlled. Her thyrotoxicosis remained under satisfactory control on daily doses of thiouracil varying from 0.2 to 1 gm. for 5½ months. During this time she gained 31 pounds, but her insulin requirement increased. After 5½ months of treatment with thiouracil she required 30 units of protamine and 25 units of unmodified insulin in the morning and 25 units of unmodified insulin in the evening to prevent glycosuria on a diet containing 120 gm. of protein, 120 gm. of fat and 260 gm. of carbohydrate. Her fasting blood sugar at that time was 122 mg. per 100 cc.

. Several possible factors may have operated in the case to prevent the amelioration of the diabetes which might have been expected to accompany the improvement in the thyrotoxicosis. Such factors might include progressive growth, the onset of menstruation which occurred while she was under treatment, and possibly the production of increased diabetogenic activity in the anterior pituitary by thiouracil. Failure of the diabetes to improve concomitantly with the control of the thyrotoxicosis is in contrast to the usual amelioration of diabetes when associated thyrotoxicosis is controlled by irradiation or thyroidectomy.

Comment. Our experience with thiouracil in the prolonged treatment of thyrotoxicosis agrees in general with that reported by other observers. We have likewise encountered the same types of complications and toxic effects as have been reported elsewhere. Among these, neutropenia with associated pharyngitis and fever appears to be the only one of major importance. The failure of exophthalmos to recede in our cases, and its occasional aggravation following thiouracil, do not confirm some other observations. (See footnote, p. 562.) Thyrotoxic patients do not seem to become refractory to thiouracil, and those who relapse when the drug is withdrawn can apparently be brought under control repeatedly by its readministration. The ability of most patients to remain ambulatory, or even to continue at work,

while under treatment for long periods of time constitutes an important advantage. Bed rest at initiation of treatment shortened the time of response. Examination of our patients who failed to respond satisfactorily shows no apparent common factor. However, such factors as pregnancy, myasthenia gravis, prolonged iodization prior to treatment and a possible background of a larval Cushing's disease existed in 4 cases. In Case 5 it is possible that a more prolonged period of treatment with thiouracil might have produced a better response. In Case 3 the patient's refractoriness to the resumption of thiouracil may have been due to an underlying hyperfunction or dysfunction of the anterior pituitary.

A number of important questions remain to be answered regarding the effect and clinical usefulness of thiouracil. Among these are:

1. What late toxic effects may follow its prolonged use? Is it possible, for example, that depression or exhaustion of the bone marrow might follow the prolonged ingestion of the drug in some cases?

2. What undesirable dislocations of endocrine relationship might be induced by prolonged inhibition of thyroid hormone production and the consequent disturbance of thyroid-pituitary balance? Is there thus a possibility that hyperfunction of the pituitary might eventually be produced, or that pituitary exhaustion might ensue? Is it possible that the maintenance of a chronically hyperplastic state of the thyroid might be followed by fibrosis, or atrophy, or neoplastic change?

3. What is the effect of thiouracil upon the structure and function of the normal human thyroid? Observations reported to date on such an effect are inadequate. Much further work appears desirable in an effort to explain the discrepancy between the consistent effects of thiouracil in normal lower animals and its apparent lack of effect on the normal human. Our observations in Case 8 suggest the possibility that there may be some action upon the normal human thyroid which might prove of considerable therapeutic value in congestive heart failure and certain other disorders.

4. What types of thyrotoxicosis will respond best to thiouracil, and how long must such cases remain under treatment before a permanent cure is effected?

5. Could the therapeutic response in thyrotoxicosis be enhanced by the coincidental use of antipituitary agents such as irradiation, estrogens or androgens?

The observation of many more cases over a much longer period of time will be necessary before these questions can be answered, and before the usefulness of thiouracil can be ultimately evaluated. Evidence available at present would appear to justify the tentative conclusion that thiouracil may be useful: (*a*) in the preoperative preparation of patients with severe or complicated thyrotoxicosis, and (*b*) in the prolonged treatment of patients with mild or moderate uncomplicated thyrotoxicosis.

The failure of some of our patients to respond to thiouracil raises again the possibility that certain types of thyrotoxicosis may be the

result of dysthyroidism rather than hyperthyroidism. This concept was suggested by Plummer[7] in an effort to explain what he believed to be the unresponsiveness of patients with toxic nodular goiter to iodine. The theory of dysthyroidism (that is, a toxic state resulting from the production of an abnormal hormonal product of the thyroid gland rather than an excess of a normal hormonal product) has received little attention in recent years. It is, however, supported to some extent by the following evidence: (*a*) Complete and lasting reproduction of the thyrotoxic syndrome as it exists in man cannot be achieved experimentally either by thyroxinization or by the administration of anterior pituitary hormones. (*b*) A number of clinical and experimental observations suggest that certain types of goiter may exert a specific cardiotoxic influence without producing a typical thyrotoxic syndrome.

It is conceivable that the failure of certain thyrotoxic patients to respond to thiouracil might be due to the fact that their toxicity is due to an abnormal thyroid hormone, and that the production of such an abnormal hormone cannot be interrupted by thiouracil.

Although toxic goiters do not usually become smaller during the first few weeks of thiouracil therapy, Williams and Clute[11] have reported definite reduction in size of the goiters in several of their cases after prolonged treatment. We have likewise observed this reduction in size in 8 of our patients after periods of treatment varying from $2\frac{1}{2}$ to 9 months. It has been suggested[8] that such late reduction in size might be the result of exhaustion atrophy or fibrosis. However, it also seems possible that exhaustion of thyrotropic hormone production by the anterior pituitary might be a factor. This possibility could be investigated by measurement of the urinary excretion of thyrotropic-pituitary hormone in patients showing such reduction in size of the thyroid.

Summary and Conclusions. Clinical experiences with 37 cases of thyrotoxicosis treated with thiouracil have been described. Thirty patients (81%) showed a favorable response, 4 (10.9%) showed a partial response and 2 (5.4%) showed no response to treatment. Three of the 6 patients showing unsatisfactory response presented associated conditions which may have influenced their reactions.

In 4 patients thiouracil was used during preparation for thyroidectomy. One of these died 20 hours after operation, but thiouracil was not regarded as a factor in his death. Necropsy in this case showed no lesions which could be associated with the use of thiouracil.

The control of thyrotoxicosis with thiouracil in a 13 year old girl with diabetes mellitus was not followed by an increase in her carbohydrate tolerance or a decrease in insulin requirement.

The histologic appearance of the thyroid gland in our patients prepared for thyroidectomy with thiouracil showed the hyperplasia and other changes previously reported by others.

Eight patients have remained in remission for periods varying from 3 weeks to 7 months following the complete withdrawal of thiouracil;

on minimal doses (0.1 to 0.2 gm. daily) 3 patients have responded likewise. Thirteen patients relapsed when the drug was either reduced in dosage or withdrawn; all of these patients, however, again responded to readministration of thiouracil.

Measurements of cardiac output by ballistocardiogram in 9 patients showed a general tendency toward reduction in output under thiouracil therapy which was roughly parallel with the decline in basal metabolism.

No evidence of development of refractoriness to thiouracil was observed.

Untoward reactions attributable to the drug occurred in 8 patients. The most important of these was neutropenia with pharyngitis and fever, noted in 2 cases. Reduction in the size of the thyroid gland was noted in 8 patients after prolonged treatment. Exophthalmos tended either to remain stationary or to increase slightly.

While much further work remains to be done before the clinical usefulness of thiouracil can be finally evaluated, it may tentatively be concluded that this drug effectively controls most of the phenomena of thyrotoxicosis in the large majority of patients, and that its use at present is justified in the protracted treatment of mild or moderately severe cases and in the preoperative preparation of selected patients for thyroidectomy. It may also prove of considerable value in patients regarded as unacceptable surgical risks.

We are indebted to Dr. Isaac Starr for the ballistocardiographic data, to Drs. R. C. Horn and Joseph Snyder for pathologic reports, and to the Lederle Company for their generous coöperation in supplying us with thiouracil (Deracil). Measurements of exophthalmos with the Hertl Exophthalmometer were made by members of the staff of Dr. F. H. Adler, Chief of the Department of Ophthalmology.

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THE USE OF PENICILLIN IN TOPICAL APPLICATION

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With the Technical Assistance of
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Owing to the shortage of penicillin, a technique for the extraction of penicillin from the urine of patients under treatment for syphilis, gonorrhea and septic infections was developed by the author.[1] It was found practical and inexpensive, yielding 30 to 40% of the antibiotic substance administered. A considerable number of animal and clinical trials demonstrated that the reclaimed penicillin was non-toxic and non-pyrogenic when used parenterally. Dosages as high as 2,000,000 units a week were administered intramuscularly with excellent clinical results, differing in no way from therapy with commercial penicillin. We have decided therefore that the reclamation of penicillin is a useful means of economizing the substance under conditions of scarcity. No noteworthy information concerning the effectiveness of penicillin therapy in infections can be added from this experience to the data presented by Keefer and his co-authors.[2] However, the availability of the material has encouraged us to make certain observations concerning the use and desirability of topical applications.

It has been observed that penicillin administered intramuscularly or intravenously rapidly permeates the body fluids, excepting the spinal fluid, saliva and tears.[3] Clinical observation made us believe that the nasal accessory sinuses and the skin may frequently be inadequately treated even with high dosages given by the intramuscular route. Two cases illustrate this point.

Case Reports. Case 1. P. T., a 20 year old male with chronic rheumatic endocarditis, was under treatment for *Streptococcus viridans* septicemia, receiving 360,000 to 500,000 units of penicillin daily for 25 days. This case will be reported in a separate paper. The bacteremia was controlled and the constitutional improvement was excellent, but the patient had considerable nasal discharge from which *Strep. viridans* was cultured. The frontal and maxillary sinuses appeared abnormally opaque in roentgenograms. A saline dilution of penicillin, 1000 units per cc., was sprayed into the nose at frequent intervals with a nasal atomizer. In this way about 20,000 units of penicillin were administered daily. Penicillin was excreted in small amounts in the urine during this therapy. The clinical effect was good and nasal discharge became scanty after 5 days.

Case 2. W. K., a 70 year old male, was treated with 200,000 units of penicillin by intramuscular injection daily for 30 days, in a clinical trial to determine the effect of the antibiotic on his disease, squamous carcinoma of the skin. At the end of this period, staphylococci were readily detected in biopsy sections in crypts of the tumor. Penicillin was subsequently administered by topical application with electrophoresis and the organisms were not to be found after the first day of treatment. The patient's thumb was being exposed to a solution of 5000 units per cc. with a 5 ma. current passed through it. A 30 minute treatment resulted in absorption of penicillin, as demonstrated by the excretion of about 1 unit per cc. of urine during the subsequent 4 hour period.

Observations concerning the employment of penicillin in the control of gingivitis and Vincent's infection of the mouth are being made and will shortly be published by Strock.[4] The clinical effectiveness of 5000 units of penicillin applied as a mouth irrigant once a day is as great as that of large intramuscular doses. The absence of penicillin in the saliva after parenteral administration was noted by Rammelkamp.[3]

The use of an ointment for maintaining a local supply of penicillin on the skin was suggested by Clark, Colebrook, Gibson and Thompson,[5] Florey and Florey,[6] and Bodenham.[7] Since doubt was felt concerning the release of penicillin from an ointment base, the following *in vitro* tests were performed:

Two ointments were prepared, one with lanolin as a base and the other using a vanishing cream base, each containing 1000 units of penicillin per gm. One batch in vanishing cream base had Aerosol MA added in amounts of 0.1 and 1%. Other penetrating and wetting agents (Triton and Duponol C) were also tried. Since none of these mixtures exceeded the effectiveness of 0.1% Aerosol MA, subsequent experiments were standardized on this. A 1.5% agar medium was inoculated heavily with *B. subtilis*, and after thorough agitation was transferred to tubes. After cooling and solidification, the surface of each tube was covered with a thin layer of one of several materials under test, and the depth of inhibition was measured from the line of contact to the layer of bacterial growth (Fig. 1). The results follow:

Tube	Contents	Bacterial inhibition
1	Ointment base with Aerosol 0.1%	None
2	Laonlin with 1000 units penicillin per gm.	6.0 mm.
3	Penicillin solution, 1000 units per cc.	16.5 mm.
4	Ointment with Aerosol and 1000 units per gm.	15.0 mm.
5	Above ointment without Aerosol (not illustrated)	13.0 mm.

The conclusion reached from these observations which were repeated several times was that in a suitable ointment base penicillin when applied topically has a considerable ability to penetrate a solid agar culture medium, and penetration is enhanced by the addition of a wetting agent (Aerosol).

A second experiment was designed to demonstrate any penetration of penicillin applied as an ointment through tissue. The technique was as follows:

Technique. Short lengths (5 to 7 cm.) of wide glass tubing (12 mm.) were covered over one end by pieces of fresh skin obtained at circumcision operations. The cutaneous surface was toward the tube lumen, and the tubes were partially filled with the material under test. Each tube was then placed firmly over an agar culture seeded with *B. subtilis* in a test tube wide enough to admit the skin-covered tubing. There was no evidence of inhibition of bacterial growth through the skin layer whether by aqueous dilutions of penicillin up to 1000 units per cc., or by ointments containing a similar concentration of penicillin, both with and without wetting agents.

As a check on the failure of these *in vitro* attempts to demonstrate penetration, 25,000 units of penicillin were applied as an inunction in

ointment with Aerosol. Urine was collected for the 4 hour period following inunction and failed to demonstrate any penicillin content within the range of our test (0.3 unit per cc.). Further attempts with higher penicillin dosages are being made, but it is apparent that diffusion through the skin is certainly too small for therapeutic utility.

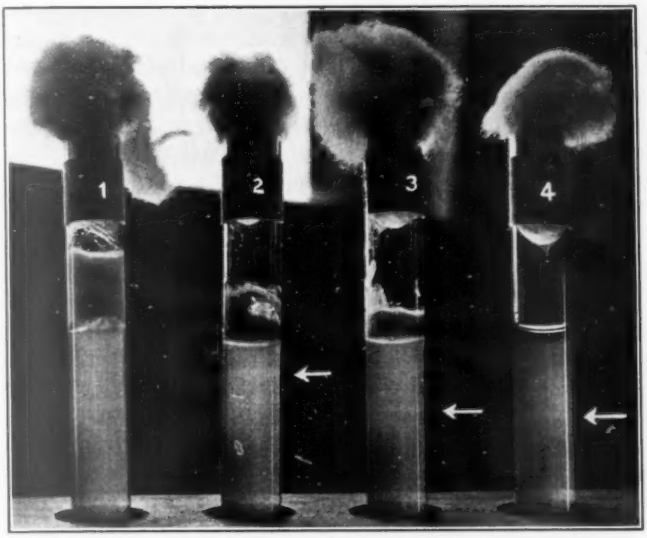

FIG. 1.—Penetration of penicillin through agar from 3 media. The tubes contain: *1*, vanishing cream ointment with Aerosol 0.1%; *2*, lanolin containing 1000 units penicillin per gm.; *3*, ointment with Aerosol containing 1000 units penicillin per gm.; *4*, aqueous dilution of penicillin, 1000 units per cc. The penetrating ability of penicillin is almost as great in the ointment base with Aerosol as in aqueous solution.

Clinical use of the penicillin Aerosol vanishing cream ointment has been made in a number of types of cases, as follows:

Diagnosis	Duration	Results
1. Sycosis barbæ	3 wks.	Excellent in 2 days
2. Sycosis barbæ	5 wks.	Excellent in 4 days
3. Furunculosis	6 days	Good
4. Furunculosis	4 days	Good
5. Furunculosis	11 days	Good
6. Furunculosis	3 days	Good
7. Furunculosis	3 days	Good
8. Chronic cellulitis; ulceration (postop. osteomyelitis)	9 mos.	Good
9. Chronic cellulitis; ulceration (postop. osteomyelitis)	7 mos.	Good
10. Indolent ulcer (symbiotic infection)	4 mos.	Improving (2 wks.)
11. Chancroid	1 wk.	Excellent in 7 days

The appearance of a zone of infection under treatment by the ointment is characterized by hyperemia and arrest of suppuration. In an uncomplicated situation, like a furuncle, the first change is seen after 24 hours in a lessening of the peripheral edema and reduction in tension of the lesion. Early furuncles resolve in 4 to 6 days, but suppurating ones will go on to evacuation. Chronic pyogenic infections

respond slowly and develop a considerable zone of hyperemia when the ointment is applied for extended periods. The granulation tissue growth is accelerated and the surface becomes engorged. Similar observations have been made by Bodenham.[7]

Discussion. In his review of his discovery of penicillin, Fleming[8] makes the comment that "perhaps the most important use of penicillin is locally in more or less minor infections and not in the dramatic cases in which patients are snatched back from death." The observations made here tend to emphasize the use of topical penicillin application. When consideration is given to the difficulty and expense of maintaining over a period of many days or weeks a high penicillin concentration by parenteral administration, topical applications, when practicable, offer a suitable alternative. It is possible to reach local levels of penicillin activity by topical administration far in excess of the highest ranges we have maintained by intravenous and intramuscular use, namely 0.7 to 0.9 units per cc. of blood achieved by continuous introduction at the rate of 20,000 units per hour. There are many bacteria, including some strains of staphylococci, which are resistant to low penicillin concentrations, or even to the high levels noted above, but are susceptible at still higher levels. For the control of such infections, penicillin may be applied topically or by both parenteral and topical routes. Pereyra and Landy[9] noted the failure of ordinary doses of penicillin administered intramuscularly to affect chancroid. On the other hand, local application of penicillin ointment has been more rapidly curative than treatment with sulfonamides.[10]

Summary. 1. Evidence is cited indicating that penicillin administered parenterally may not reach a sufficient concentration in certain regions for therapeutic effectiveness. Topical application in such regions has, in several instances, been successful.

2. Penicillin incorporated in a suitable ointment, together with a wetting agent, penetrates agar sufficiently to cause inhibition of *B. subtilis* at a depth of 16 mm. Although it does not demonstrably penetrate through a skin layer *in vitro*, penicillin in such an ointment base has, in our experience, strikingly effective value in acute and chronic pyogenic infections of the skin and subcutaneous tissues, particularly in sycosis barbæ, infected superficial wounds and furunculosis.

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PENICILLIN

WITH SPECIAL REFERENCE TO ITS USE IN INFECTIONS COMPLICATING DIABETES*

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THE efficacy of penicillin in treatment of certain types of pyogenic infections, together with its remarkable lack of toxicity, suggested that the drug might be particularly useful in the management of some of the more localized and generalized coccic infections so frequently encountered in association with diabetes mellitus. Chemotherapy with sulfonamides, as pointed out by Styron, Bromley and Root,[19] while of undoubted value in controlling the extension of infections, cannot be expected to cure necrotic lesions such as carbuncles and gangrene. The experience here described began when penicillin was still a laboratory curiosity, and because supplies were so limited and impure, the early cases were treated by infiltration of the drug, and the patients did not receive what are now believed to be adequate doses. Nevertheless, the responses obtained by local infiltration of penicillin directly into infected areas, when compared with general administration have been so striking that it seems worthwhile to direct further attention toward this method of administration.

In 1929 Fleming[5] made his observation that around a large colony of *Penicillium notatum* which accidentally contaminated one of his culture plates of staphylococcus, the colonies became transparent. Instead of discarding the contaminated plate, Fleming's curiosity was aroused and he endeavored to find out what it was in Penicillium that brought about this antibacterial action. Subsequent experiments showed that the active substance was soluble and filterable and that it had activity against staphylococci, hemolytic streptococci, pneumococci, gonococci and *Bacillus diphtheriæ*, but not against *B. coli* or *B. influenzæ*. During the next decade the sulfa drugs were developed and it was not until 1940 that Florey and his group[3] at Oxford discussed penicillin, as the active substance had been termed, as a chemotherapeutic agent.

By 1941, 10 clinical cases unresponsive to the usual chemotherapeutic agents had been accumulated,[1] and great interest had been aroused in the new antibiotic agent. Thus, discovery of penicillin and its recent intensive development for therapeutic use were both due to British scientists, Fleming and Florey and their collaborators at Oxford.

The research leading up to the large-scale production of penicillin may well be claimed as an instance of collaboration without parallel in the history of the pharmaceutical industry. Collaboration has been

* Presented April 11, 1944, before the Medical Society of the County of Oneida, Utica, New York.

freely carried out between scientific workers in both industrial and academic fields. There has been complete mobilization of all the skill and knowledge in both Britain and the United States for speeding the solution of problems of manufacture of this most unusual drug, as well as complete coöperation in solving the clinical problems presented in determining how penicillin may best be applied in the actual treatment of patients. In 1943 Chester Keefer[11] as Chairman of the Committee on Chemotherapeutic and Other Agents, National Research Council, and his co-workers correlated and reported on the results of treatment by a group of 22 accredited clinical investigators, and the value of penicillin was completely established. It remained to increase production sufficiently to permit the widespread application of the drug to the treatment of infections, both civilian and military. This is now well on the way to final accomplishment.

Production of Penicillin. The cost of producing the early small batches of penicillin was tremendous, but the vital importance of the drug in war medicine has been an ever-present incentive to rapid improvement of methods.

Intensive chemical study has already shown results by improving yield, purity and concentration, and has even lent encouragement to efforts directed toward ultimate synthesis of the drug. At present it must still be prepared by cumbersome biologic methods and, consequently, penicillin is of a more or less variable nature and there is no absolute certainty that different batches will have the same standard activity per milligram of solid material.

The main steps in the production of penicillin are first growing the mold under conditions optimal for greatest yield, separation of the active principle from the mold, and its adsorption and chemical purification and concentration. The solution is then frozen and dried under a vacuum. The dry material is pulverized, assays are conducted to determine the number of units per milligram, toxicity tests are performed, and the powder is finally packaged in a dry state for distribution under the regulations of the War Production Board.

Assay. One of the earliest problems encountered was to determine the strength of penicillin. The cup plate or its variant, the cylinder plate method, and the serial dilution method are the procedures commonly employed. Techniques have been developed by Foster,[7] Rammelkamp,[14] and Abraham, Chain *et al.*[1] When the latter observers first studied penicillin they prepared a reference standard to be used in evaluating new preparations and, furthermore, they established the Oxford unit (or as it was formerly termed the "Florey" unit) which is defined as "that amount of penicillin which when dissolved in 1 cc. of water gives the same inhibition as this standard." The standard referred to gave a zone of inhibition having an average diameter of 24 mm.

Pharmacology. Florey[6] found that the penicillin solutions as used therapeutically are bacteriostatic rather than bactericidal. Penicillin is not inactivated by pus, blood, serum or tissue autolysates, and leukocytes and tissues are not harmed by concentrations far greater

than those used therapeutically. Some reactions have been observed, but these seem most likely to be caused by impurities rather than penicillin itself. Those noted have consisted of fever, chills, thrombophlebitis at the site of injection, urticaria, localized tenderness about the site of injection, headache, flushing, tingling in the testes, and muscular pain. Probably the occurrence of such symptoms will become even less frequent as greater and greater purity is obtained.

Hamre *et al.*[8] found the lethal intravenous dose to be about 90,000 to 250,000 units per kilo in mice, depending upon the purity of the sample. Robinson[18] found that doses of 600,000 units per kilo were not lethal when given intravenously to mice. Such results indicate that further purification, or preparation of the drug as a synthetic chemical substance, may possibly be associated with even more complete freedom from toxicity. There is, of course, some variation in species toxicity, as shown by the fact that acute toxicity is induced in guinea pigs and rabbits with doses that are much lower.[8] The lack of clinical toxicity of the drug has been one of its most striking characteristics.

Penicillin is rapidly absorbed and quickly eliminated following its intravenous injection.[17] Fifty-eight per cent of it can be recovered from the urine. It diffuses readily through the tissues but does not penetrate the subarachnoid space. Unfortunately penicillin is rapidly destroyed in the gastro-intestinal tract and, consequently, its oral administration is not practical. Rectal administration is also ineffective owing to the inactivation of the drug by coliform bacilli which are thought to act through production of penicillinase. Excretion by the kidney proceeds so rapidly that, following a single intravenous injection, it is often impossible to detect penicillin in the blood longer than 3 or 4 hours. Dawson and Hobby[4] point out that 90 per cent of the injected material has disappeared in 30 minutes, while the remaining 10% requires 3 or 4 hours before complete elimination. Consequently, single intravenous injections must be given frequently, at least every 3 or 4 hours over the day and night, or administration must be continuous by intravenous drip. Following intrathecal or intraärticular or intrapleural administration, penicillin has been demonstrated for as long as 24 hours.[16] The drug is not normally excreted into the spinal fluid.[15]

It is well known that organisms sometimes become resistant to sulfonamides and this likewise is true of penicillin,[13] but rarely is an organism resistant to both drugs. The action of the two therefore must be fundamentally different, and this may have a practical bearing on therapy of diseases such as chronic osteomyelitis, staphylococcus septicemia and the like. Most of the gram-negative bacilli are resistant.

Indications. In general, penicillin is indicated in the treatment of all infections with gram-positive organisms and gram-negative cocci, but is useless in infections caused by gram-negative bacilli. Consequently it is important to determine the type of organism present. The 500 cases reported by Keefer[16] included many that had failed to

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respond to the sulfonamides, including *Staph. aureus* bacteremia and local infections with staphylococci and pneumococci; streptococcal, staphylococcal, and pneumococcal meningitis and empyema; pneumococcic pneumonia; gonococcic infections; and subacute bacterial endocarditis. The results in the latter have been disappointing but, more recently, Loewe *et al.*[12] treated 7 consecutive patients by means of the combined administration of penicillin and heparin with uniformly successful sterilization of the blood stream and relief of clinical manifestations.

Administration. Penicillin is very soluble and under aseptic conditions may be dissolved in sterile water, or preferably in cold sterile normal saline solution, so that the final concentration is from 5000 to 20,000 units per cc. The solution should be kept cold in the refrigerator at all times, and the material to be used as soon as possible after dilution, at the longest within a few days. Further dilutions are made from the ampoule according to the route of administration and the dose to be given. For systemic effect injections should be intravenous or intramuscular, as subcutaneous administration tends to be painful. There is no general agreement as to the best method of administration, as indicated in the recent articles.[2,4,9] Local infiltration of solutions having concentrations of from 100 units to 1000 units per cc. has not caused enough pain and discomfort in the present series to interfere in any way with the use of the drug.

In general, the published work seems to indicate that much more material is required for treatment by intramuscular or intravenous routes than is the case when the drug can be given topically (this includes intraärticular, intrathecal and intrapleural administration). My own personal observations thus far have shown the desirability, and sometimes the necessity, for local administration directly into the infected area, and when this has been possible, recovery has been more prompt and has occurred with much lower dosage.

Dosage. Penicillin is so soluble that as much as 100,000 units can be dissolved in 1 cc. In general, dosage ranges between 30,000 and 100,000 units daily, depending upon the type of infection. It has been helpful to test out the sensitivity of the organisms wherever possible, and in any event it is essential to know with which organism one is dealing. Recently, there has been less tendency to begin with large initial doses, and often only the first dose is given intravenously, although some observers still prefer to administer at least the first 24 hour treatment by intravenous drip. Dawson and Hobby[4] emphasize that the first dose need be no larger than subsequent doses, and that larger doses are not necessary in the presence of bacteremia and in cases without bacteremia. Lastly, in general sepsis and for local therapy, the intramuscular route is generally recommended.

As yet, complete dosage schedules have not been entirely worked out for all diseases and the amounts given naturally are those which have been found effective in the treatment of cases of that particular class and do not necessarily imply that final conclusions have been reached.

The early material* used was of weak potency, not very pure, and was not regarded as suitable for administration intravenously. Consequently, localized infections were first chosen for treatment and the solutions employed ranged in strength from only 100 to about 250 units per cc. These solutions were infiltrated into the area of infection with considerable success and, even with this early material, several cases made astonishing recoveries. The method seemed particularly useful in the management of carbuncles, and several cases have responded dramatically and, in certain instances, have even gone on to resolution without formation of a slough. As penicillin became more highly purified and available in higher concentrations, cases have been treated by general administration of the sodium salt with good results, although personal experience still indicates the desirability of depositing penicillin directly into the infected tissues where accessible. In some cases of carbuncle, intravenous or intramuscular administration has been inadequate, and supplementary injections by means of a long needle directly into the necrotic mass has resulted in rapid clearing of the lesion. Penicillin requires several hours' contact with the organism to exert its full effect, and mere irrigation is not enough. Where a sinus presents, as in certain cases of osteomyelitis, satisfactory results have been obtained by forcing a few cc.'s into the tissues with a syringe every 3 hours, then preventing drainage by application of adhesive tape. Local injection in this manner seems much more economical than general administration of the drug.

Report of Cases. CASE 1. L. J., age 58, white female, admitted for a discharging infection of the right great toe and foot. Diabetes known since 1936. The infection began several months previously after cutting a thick callus which would not heel. Temperature varied from 97° to 101° F. White blood count, 10,800; urine sugar, 4+; blood sugar, 291; acetone and diacetic acid, negative. Roentgen ray disclosed no evidence of bone destruction. Under conservative management drainage of pus continued but the diabetes was easily controlled by a diet of C–120, P–80, F–100 = 1780 calories, with 15 units of protamine zinc insulin and 10 units of regular insulin, both given before breakfast; later shifted to a mixture of 10 units of protamine zinc insulin and 10 units of unmodified insulin. One month later Roentgen ray showed much more demineralization and an actual destruction of the bone of the adjacent articular surfaces of the great toe and also the sesamoid bone. A recheck in three weeks indicated further progress of osteomyelitis (Fig. 1). Drainage was established surgically by incision over the ball of the foot toward the great toe. No sequestrum was found. Healing of the incision was prompt but there remained three sinuses draining copiously which gave *Staph. albus* on culture.

Course. Penicillin (200 units per cc.) was injected into each sinus every 4 hours, closing the opening with sterile adhesive tape in order to prevent escape of the drug. Although only a few cc.'s total could be infiltrated, drainage ceased within 2 days, one sinus closed and was followed by the second 3 days later. The last sinus persisted for 2 weeks before finally closing, at which time Roentgen ray showed filling in of the bone at the original site of the lesion. The patient was discharged with complete healing. Total dosage, approximately 20,000 units.

* Supplied by Dr. J. M. McGuire, Lilly Research Laboratories. In later cases both the sodium and calcium salts of penicillin have been employed without apparent significant difference in response.

CASE 2.—W. M., age 63, white male, admitted complaining of an infected foot and diabetes. One toe had been removed a year previously for infectious gangrene. There was a low-grade fever. Culture from the draining area was predominantly *A. ærogenes* and streptococcus (non-hemolytic); blood sugar ranged from 142 to 165 mg. per 100 cc., while taking a diet of C–190, P–80, F–90 = 1890 calories without insulin.

FIG. 1.—Case 1. *A*, *B*, Progress of destructive lesion; *C*, after healing.

Course. The foot was elevated in bed, irrigations with Dakin's solution were instituted and sulfathiazole administered in full dosage. Under this management the cellulitis regressed, but Roentgen ray examinations gave evidence of a destructive bone lesion involving the first metatarsal. Healing did not occur and the sinus continued draining profusely.

Treatment with penicillin (200 units per cc.) was begun by filling the sinus cavity every 4 hours and preventing loss by closing the opening with sterile adhesive tape. At first the capacity was several cc., then gradually the amount lessened as healing progressed. In 2 weeks Roentgen ray showed definite improvement, drainage had ceased, and it was no longer possible to infiltrate appreciable amounts of the drug, so it was discontinued. Complete healing ensued. Total dosage, approximately 30,000 units.

CASE 3.—G. G., age 44, white male, admitted with a large carbuncle of the neck 6 inches in diameter of 1 month's duration. Previous symptoms of diabetes extended only since onset of the infection. Blood sugar, 320 mg. per 100 cc.; urine sugar 4+; acetone and diacetic acid, negative.

Course. Diabetes was controlled by a diet of C–150, P–70, F–100 = 1780 calories, with 40 units of protamine zinc insulin before breakfast and a supplementary dose of 10 units of unmodified insulin. Fever daily ranged to 102° F., the white blood count was 13,000 and there was no response to intensive therapy with sulfathiazole. As the surgical department considered the lesion inoperable, five therapeutic Roentgen ray treatments were administered and were followed by some softening in the center of the lesion which, nevertheless, continued to extend rapidly until it involved the right aural region, the lower part of the face, and produced paralysis of the facial nerve. Blood culture was negative, smears and cultures of the pus showed a mixed growth

A

B

FIG. 2.—Case 3. Carbuncle. *A*, Before infiltration of penicillin; *B*, 2 weeks after local treatment with 50,000 units of penicillin.

with *Strep. hemolyticus*, *A. ærogenes*, and gram-positive cocci predominating. The patient was severely toxic and after 2 weeks appeared moribund, with a septic temperature reaching 105° F. (Fig. 2).

A rather crude penicillin solution (about 200 units per cc.) was infiltrated into the necrotic tissue by means of a long needle through the multiple draining sinuses and injections were repeated at 4-hour intervals (20 to 30 cc. doses). Response was prompt and dramatic, the temperature falling to normal within 24 hours. At the end of a week the patient was put in a wheel chair owing to a large decubitus ulcer over the back and sacrum, although he was still very weak and evidenced mental aberration. Softening of the carbuncle occurred rapidly and excess necrotic tissue was removed surgically connecting draining sinuses. The insulin requirement fell to 20 units of protamine zinc insulin once daily. The area on the neck soon filled with healthy appearing granulation tissue (Fig. 2*B*) but the large decubitus lesion continued to spread and eventually formed a great slough. The patient refused to eat, became progressively weaker and, after being maintained by intravenous infusions for almost two weeks, finally died.

That some of the locally infiltrated solution of penicillin was absorbed generally was shown by finding traces of penicillin in the urine. Had it been available, earlier administration of a suitable concentration for its general effect might well have prevented the ultimate outcome. Total dosage, about 50,000 units.

Case 4.—C. B., age 43, white female, admitted for furunculosis. A known diabetic for 10 years the patient had received no treatment for 5 years. Four weeks previously she developed multiple furuncles over the back, two of which persisted and had now reached a size of about 1 by 1½ inches in diameter. White blood cells, 4950; blood sugar, 420; urine sugar, 4+; acetone, 1+. Culture from the pointing furuncles disclosed *Strep. hemolyticus* and gram-positive cocci.

Course. Taking a restricted diet, C–120, P–80, F–90 = 1610 calories, the fasting and postprandial blood sugar levels were controlled with 20 units of protamine zinc insulin and 30 units of unmodified insulin before breakfast with 15 units of insulin before the evening meal. All four period urine specimens became negative for sugar and insulin dosage was reduced to 30 units of protamine zinc insulin and 15 units of unmodified insulin, then control was continued with a single injection of a 2 to 1 mixture consisting of 10 units of protamine zinc insulin and 20 units of unmodified insulin in the same syringe. Blood sugar levels averaged 80 units per cc. fasting, 131 units per cc. postprandially.

In this instance penicillin of somewhat higher potency (250 units per cc.) was injected locally into each furuncle three times daily for 8 days. Only 1 or 2 cc. could be injected, but there was rapid and complete regression of the two localized lesions and the patient was discharged completely healed. Total dosage, 12,000 units.

Case 5. V. T., age 49, white male, admitted for a carbuncle of the neck of 20 days' duration. Sugar had been found in the urine at a previous industrial examination. The "boil" was incised 10 days previously but continued to spread and the lesion was now 18 by 12 cm. with a small skin opening in the center, draining copiously. Blood sugar, 314; urine sugar, 4+; acetone, negative; white blood count, 15,200; temperature, 100.6° F. Pus from the sinus cultured *Staph. aureus*. Retinal examination showed many fresh hemorrhages and typical exudates.

Course. The patient was given a diet of C–120, P–60, F–80 = 1440 calories, and fasting and postprandial levels and the four period urine specimens were well controlled with 30 units of protamine zinc insulin and 15 units of unmodified insulin, both given before breakfast, then doses were transferred to a 2 to 1 mixture of 12 units of protamine zinc insulin and 24 units of unmodified insulin with perfect control. During the interval the patient had a daily chill and elevation of temperature of 101° to 102° F. without positive blood culture. Penicillin (200 units per cc.) in 10 cc. amounts was introduced into

the mass locally three times daily, for 2 weeks. The lesion responded rapidly and healed without any slough whatever. A purplish discoloration was evident over the site of the carbuncle for about a month after discharge from the hospital. Total dosage, 52,000 units.

CASE 6. M. W., age 55, white female, admitted in semistupor, overwhelmed by toxemia, with a carbuncle of the left lower jaw, cellulitis of the face and diabetes mellitus. Temperature was 101° F. on admission, arose to 104°, pulse varied between 100 and 120, and respiration was 30 to 40 per minute. White blood count, 18,500; blood sugar, 320; urine sugar, 3+; acetone and diacetic acid, negative; CO_2 combining power, 56. Blood culture showed positive growth of *Staph. albus* in the first 12 hours.

Course. Penicillin (100,000 units) was administered in saline and dextrose intravenously by continuous drip, on the following day and continued the day after. The cellulitis rapidly spread posteriorly and the patient was obviously moribund. It is interesting that the blood culture became negative after the first 100,000 units of penicillin had been administered. The patient died on the 3d day after admission and autopsy was refused. Dosage, 140,000 units total.

CASE 7. L. B., age 59, white female, admitted complaining of a large painful carbuncle on the back of the neck which had been lanced a week previously and continued to extend. Diabetes was discovered 10 years previously but the patient had never taken insulin. The carbuncle was 6 by 10 cm. in size. There was no fever; white blood count, 9800; blood sugar, 192; urine sugar, 2+; acetone and diacetic acid, negative. Blood culture was negative. Culture from the discharge showed *Staph. albus* and *Strep. viridans*.

Course. Sulfathiazole was administered and the diabetes was controlled with a diet consisting of C–130, P–60, F–80 = 1480 calories and a mixture of 10 units of protamine zinc insulin and 20 units of unmodified insulin, which later was changed to 30 units of clear histone zinc insulin. Fasting and postprandial blood sugar levels were held within normal limits and the urine remained sugar-free in all 4 daily specimens. Two Roentgen ray treatments were given. Progress was unsatisfactory and penicillin was administered in doses of 5 to 10 cc. (5000 units per cc.) infiltrated directly into the infected tissues through the earlier incision (Fig. 3). This was continued three times daily until 100,000 units had been infiltrated. The lesion was apparently healed but the area was still discolored at the time of discharge, 3 weeks later.

The following week a small fluctuant area was noted above the original site of the carbuncle and it was gently incised to permit drainage. It healed promptly, but during the next week several other small infected areas appeared that seemed to develop in hair follicles. These were treated with sulfathiazole cream, but succeeding crops developed. The patient was readmitted for further treatment, and was given penicillin by intramuscular injections, 20,000 units every 4 hours, then 10,000 unit doses, without any local applications. The reinfected areas subsided promptly and there has been no further recurrence.

This case illustrated the comparative efficacy of locally injected and generally administered doses. If the infection is accessible to local injection, the amount of penicillin required is far less. Total dosage in this case was almost 750,000 units.

CASE 8. R. D., age 61, white male, admitted with a history of diabetes of about 1 year's duration and a carbuncle 11 weeks old. It was a putrid, sloughing, gangrenous mass extending between both shoulders and up to the base of the neck with a deep sinus extending down almost to the spine. Chills, fever, and sweats occurred daily. The blood sugar level on admission was 354, urine sugar 4+, and acetone was positive. Smears and cultures from the pus showed a mixed infection, predominantly gram-positive bacilli and cocci. Blood culture was positive for *Staph. albus*. Serum proteins 5.7 (albumin 2.9, globulin 2.8). The patient was obviously in a terminal state and recovery seemed very doubtful (Plate I, *A*, *B*, *C*,).

A

B

FIG. 3.—Case 7. Carbuncle. *A*, Before treatment with 100,000 units by local infiltration; *B*, after treatment. Relapse 3 weeks later.

Course. Administration of penicillin was begun by giving 20,000 units diluted to 1000 units per cc. directly into the necrotic mass, entering through the opening at the center of the carbuncle by means of a long needle. Injections were made every 4 hours until a total of 400,000 units of penicillin had been administered. Progress was dramatic. The fever fell to normal, the necrotic tissues separated in a few days leaving clean granulations behind. One month later after a period of normal temperature when penicillin had been discontinued for several days, there was another chill and the temperature rose to 104°. The original area of involvement showed obvious reinfection, some new localized abscesses formed in the granulation and there was copious, purulent drainage. Another 100,000 units of penicillin was administered intravenously in the 24 hours, followed by 10,000 unit doses intramuscularly every 4 hours until another 100,000 units had been given. It was then discontinued because the patient complained of pain and would not permit further injections. However, there was no further exacerbation, and, although skin grafting was refused, progress continued without interruption until discharge. The blood culture was negative after the initial treatment, indicating that even though the injections were given into necrotic tissues there nevertheless was adequate absorption to produce a general sterilizing effect on the blood stream. Total dosage, 600,000 units.

CASE 9.—J. W., age 69, white female, admitted with advanced infectious gangrene of the left foot, and obvious sepsis. Amputation by disarticulation at the knee joint was performed 1 week later, and was followed by a rather stormy course as there was some reinfection about the site of the incision with purulent discharge, high fever, and finally a slough. After several weeks, a sinus formed over the condyle and there was a copious, serosanguineous discharge showing a mixed infection, and constant low-grade fever. Roentgen ray disclosed demineralization of the condyles and an area of destruction from osteomyelitis.

Course. Penicillin was administered in 20,000 unit doses three times daily. Within 3 days the drainage had entirely ceased and in a week the sinus was completely healed and the area over the exposed condyle was well covered with healthy-looking granulation tissues. One week after beginning treatment the injections were reduced to 20,000 units twice daily and discontinued a few days later. A total of 560,000 units were administered with an entirely successful result.

CASE 10. E. D., age 68, colored female, admitted with a mixed infection of the right foot which was swollen to twice normal size. It was bluish red; there was constant pain; temperature was 101° F.; white blood count, 12,500; blood sugar, 313; urine sugar, 4+; and no acetone or diacetic acid. Roentgen ray disclosed partial destruction of the superior aspect of the proximal phalanx of the great toe and first metatarsal, both areas thought to be the result of osteomyelitis. On account of the widespread involvement and rapid extension of the process, immediate amputation was considered, but it was decided to give the patient the benefit of the doubt, and 4 days later 100,000 units of penicillin were administered intravenously in 24 hours, followed by 20,000 unit doses intramuscularly every 4 hours.

Course. The patient's diabetes responded well to management after beginning penicillin therapy and she was maintained on a diet of C–130, P–60 and F–80 = 1480 calories, with a mixture of 10 units of protamine zinc insulin and 20 units of unmodified insulin given in the same syringe. All four urine specimens were sugar-free with normal fasting and postprandial blood sugar levels. An incision was made to enlarge the area for drainage and at this time the foot resembled a bag of pus about the size of a football. Unfortunately no photograph was taken as we considered the whole affair hopeless. Three days later, under pentothal sodium anesthesia, a large linear incision was made along the side of the foot and drainage was fully established. Fever dropped to an occasional 99° F. and the dosage of penicillin was reduced to 10,000 units every 4 hours. Steady progress was made from that point. Roentgen ray 10 days after treatment was started showed regression of the osteomyelitic

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process and actual filling in of the bone. In another 10 days the area of incision was almost filled with healthy granulation tissue, drainage had practically ceased, and with the exception of a small area of necrotic fascia, the wound was clean. This patient received a total of 1,220,000 units of penicillin.

CASE 11. A. McK., age 77, white male, admitted from receiving ward with large carbuncle of neck extending from ear to ear (Plate II, *A*); temperature ranging 101° to 103° F.; white blood count, 15,050; blood sugar, 301; urine sugar, 4+; and no diacetic acid. Blood culture was negative; the organism identified from pus was *Staph. albus*.

In view of a plentiful supply of the calcium salt of penicillin it was decided to administer only systemic doses, beginning with 20,000 units every 4 hours day and night. Blood sugar levels were satisfactorily stabilized with doses of 20 units of protamine zinc insulin and 10 units of unmodified insulin, both doses given before breakfast. The diet was C–150, P–70, F–80 = 1600 calories. All four period urine specimens were sugar-free and, after the first week, control was maintained with a single dose mixture of 12 units of protamine zinc insulin and 25 units of regular insulin, then 10 units of protamine zinc insulin mixed with 20 units of unmodified insulin.

Course. After 600,000 units of penicillin had been administered, the temperature was normal, but only slight recession of the edges of the lesion was noted. Intramuscular injections were discontinued, and local infiltration of the lesion with calcium penicillin, 10 cc. (1000 units per cc.) was substituted at 4 hour intervals. There was a prompt change for the better. The drug was continued until a total of 932,000 units had been administered, when Plate II, *B* was taken.

Case 12. A. R., age 26, colored female, had been treated at home for 8 days prior to admission for bilateral lobar pneumonia. She was in severe diabetic coma (severity index, 20); blood sugar, 435; CO_2, 14; blood pressure, 100/60; pulse, 140; N.P.N., 47; white blood count, 27,000. Initial treatment consisted of 2½ gm. sulfadiazine with the intravenous fluids, then since it was found that she had already been receiving the drug at home, 100,000 units of penicillin was administered in 8 hours.

Course. During the 10 hours the patient was under observation, 320 units of insulin were administered, the blood sugar fell to 267, and CO_2 increased to 19 vol. %. Death appeared to result from sudden cardiac failure.

CASE 13. N. R., age 77, colored male, received penicillin in treatment of a secondary infection of amputation stump, while diabetic control was established with a single dose mixture of 10 units of protamine zinc insulin and 35 units of regular insulin. Fever ranged from 99° to 102° F.; cultures from the area disclosed a mixed infection with gram-negative and gram-positive cocci, and some gram-negative bacilli.

Course. Penicillin was administered intravenously 20,000 units every 4 hours for 2 days; followed by a fall in temperature to normal and marked lessening in drainage. Doses were diminished to 10,000 units every 4 hours, until 430,000 units had been given. Although not healed, the condition of the stump was considerably improved. The insulin dosage was lowered to 10 units of protamine zinc insulin and 30 units of regular insulin mixed.

CASE 14. W. B., age 71, white male, was a mild diabetic easily controlled with a single dose mixture of 7 units of protamine zinc insulin and 14 units of regular insulin, with diet of C–180, P–80, F–100 = 1980 calories. He had a marked perianal cellulitis with a necrotic and gangrenous area extending over the tuberosity of the ischium. Fever ranged to 102° F.; white blood count, 26,600. There was no satisfactory response to full doses of sulfathiazole, and in spite of finding some gram-negative bacilli in the cultures, the infection was regarded as a mixed one, and penicillin, 20,000 units every 4 hours was given intramuscularly to a total of 500,000 units.

Course. The temperature fell promptly to normal, recession of the cellulitis occurred, and recovery was well established within a week. Although healing was not complete, the patient was sufficiently improved to permit transfer to a convalescent home. Carbohydrate tolerance improved and on discharge

the patient was receiving a diet of C–200, P–80, F–100 = 2020 calories, with a single dose of mixture composed of 5 units of protamine zinc insulin and 10 units of regular insulin.

Case 15. E. D., age 58, colored female, admitted to the ward with a carbuncle situated directly on top of the head, in area 7 by 10 cm.; white blood count, 23,950; temperature 103° to 105° F.; both eyes swollen almost shut. The causative organism was identified as staphylococcus. A diet of C–120, P–60, F–80 = 1440 calories and separate doses of 20 units of protamine zinc insulin and 10 units of regular insulin served to control blood sugar levels and eliminate glycosuria.

Course. Penicillin was given intramuscularly each 4 hours for 10 days, and while the temperature reached normal and the lesion ceased spreading, its size was not much diminished. An incision was made over the dorsum to facilitate drainage, and local injections of penicillin, 500 units per cc., brought about more rapid regression of the lesion. During this interval the diet was increased and control of diabetes was accomplished with a single morning injection of 12 units of protamine zinc insulin and 23 units of regular insulin mixed. Total dosage of penicillin, 800,000 units.

Discussion. It is obvious that with penicillin another great advance has been made in the treatment of certain infections. Penicillin has a few disadvantages as well as advantages, but none of the former are of much practical consequence and the drug is so nearly non-toxic that no one need be afraid to use it. Other than identification of the causative organism no new or difficult technique is involved in its practical application.

In contrast to the sulfonamides, which have been ineffective in the local infections, penicillin is remarkably efficacious. Cases of the infectious type of gangrene, osteomyelitis of the bones of feet, and the huge sloughing carbuncles of the diabetic are amenable to treatment, and adequate supplies to permit immediate application of the drug wherever indicated will undoubtedly result in vastly improved mortality and morbidity rates in the whole group of infections caused by susceptible organisms. It cannot be expected to restore dead tissue, but appears of especial value in the infectious type of gangrene where the circulation is intact. In carbuncles and other infections caused by staphylococci, results have been particularly striking.

In no instance have we observed any tendency toward a deleterious effect on carbohydrate tolerance, nor has penicillin administration necessitated larger doses of insulin. The presence of infection notoriously increases the insulin requirement of the diabetic, but in none of the cases described was there any unusual difficulty, the patients responding particularly well. The 3 deaths in this group of patients cannot rightly be attributed to failure of the drug. One of the carbuncles (G. G., Case 3) received too small a quantity owing to scarcity of material. Case 6 was in the terminal stages of her infection when admitted and undoubtedly had a central lesion. Case 12, in the 8th day of a massive pneumonia complicated by diabetic coma, was in a desperate condition on admission, and died within 24 hours, although making satisfactory progress in recovering from coma.

Penicillin should be of great value in the management of certain of the infections so often accompanying or precipitating diabetic coma,

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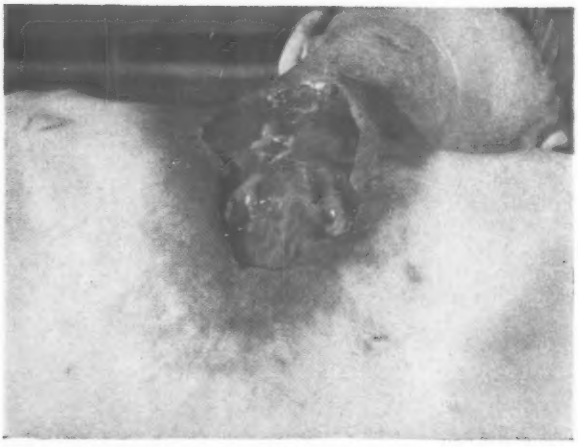
A



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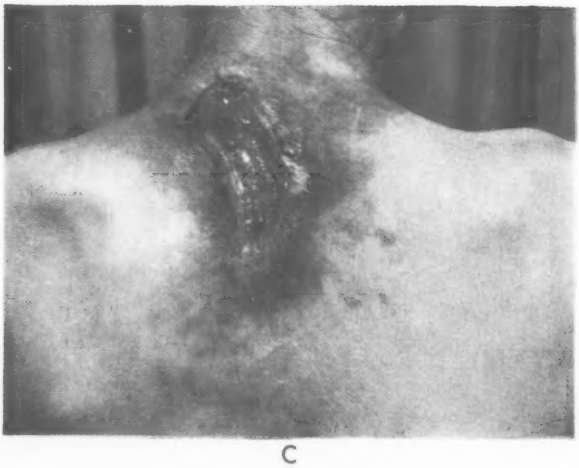

C

PLATE I.—Case 8. *A*, before treatment; *B*, after local infiltration of 400,000 units; *C*, 5 weeks later.

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A

B

PLATE II.—Case 11. *A*, Before treatment; *B*, after 932,000 units of penicillin.

since sulfonamides may precipitate in the kidney in an acid urine, and the patient in coma is often in danger from anuria in any event.

Use of penicillin does not relieve the clinician of the necessity for conducting all the other precautions necessary to proper treatment of infections. Drainage must be established surgically as indicated, since the mere administration of penicillin not only is wasteful but may not be adequate. It is essential to determine the causative organism. As experience accumulates, it will be possible to formulate more specific rules of treatment, but it is obvious already that the relatively simple clinical methods available in any hospital can be applied successfully to routine management of this form of therapy.

The rapid and sometimes dramatic response of some of the early cases of carbuncle following the injection of penicillin directly into the infected tissues is noteworthy. In Cases 11 and 15, the drug was given only by intramuscular injection until it became apparent that recovery was progressing only slowly. Almost immediate improvement appeared when injections were made directly into the infected tissues and recovery was established within a few days. The solutions used for this purpose have ranged from 100 to 1000 units per cc. of saline.

Conclusions. Penicillin is an invaluable adjunct to treatment of infections caused by susceptible organisms, and is well adapted for use in the pyogenic infections, such as carbuncles, so frequently complicating diabetes mellitus. Experience in the 15 cases presented suggests that it may be more effective if given locally directly into infected tissues than if injected parenterally for systemic effect. No direct influence on the patient's requirement for insulin has thus far been observed.

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THE TREATMENT OF MENINGOCOCCIC MENINGITIS WITH SULFAMERAZINE*

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Sulfamerazine (2-sulfanilamido-4-methylpyrimidine) has been shown to be an effective therapeutic agent, both in experimental infections in laboratory animals[9] and in clinical infections in man.[3,6,7] When administered orally, it is rapidly and efficiently absorbed, leading to higher and more sustained blood levels than those obtained with similar doses of sulfadiazine.[5] Toxic reactions to the drug have not appeared to be more frequent or more serious than those following the use of sulfadiazine.[2,10]

Recently, we have treated with sulfamerazine a large group of patients with various bacterial diseases;[1] 56 patients in this group had meningococcic meningitis. The purpose of this paper is to report in detail the results in this disease.

Since this study was undertaken, several reports have been published indicating that the use of sulfamerazine in meningococcic meningitis is followed by results as favorable as those obtained by the use of sulfadiazine.[4,6,8]

Clinical Material. The pertinent data concerning each patient are presented in Table 1.† Forty-one patients were adults and 15 were children 12 years of age or younger. In the adult group, the ages ranged from 13 years to 65 years; 34 were under 40 years of age; only 2 were over 60 years of age. Among the children, the ages ranged from 1 year to 12 years. Four were 2 years of age or younger. The average age for the group was 6 years.

All the patients presented the typical clinical picture of meningitis, and in each case the diagnosis was confirmed by bacteriologic studies. Fifty patients had gram-negative diplococci in stained preparations of the spinal fluid. In 32 of these cases, meningococci were also cultured from the spinal fluid. Positive cultures were obtained from the spinal fluid of the 6 patients in whom no organisms could be identified in stained preparations. Twelve patients had positive blood cultures. Typing of the meningococci which were isolated was not performed.

The severity of the illness varied: 13 patients (23%) were regarded as mildly ill; in 24 (43%) the illness was of moderate severity; 19 (34%) were severely ill. The patients in the last group were either comatose or nearly so. A petechial rash was observed in 34 patients (61%).

Method of Treatment. The usual dosage of sulfamerazine employed in the adult group was an initial dose of 2 gm. orally followed by a maintenance dose of 1 gm. every 8 hours. In children, dosage was calculated on a basis of 1 gm. per 20 pounds of body weight per day. Comatose patients and those who were otherwise too ill or uncoöperative to take medications by mouth were given

* This study was supported by a grant-in-aid from the Sharp & Dohme, Inc. They also supplied the sulfamerazine.

† These patients were treated at the Evans Memorial and John C. Haynes Memorial of the Massachusetts Memorial Hospitals and at the Boston City Hospital.

TABLE 1.—PERTINENT DATA ON 56 CASES OF MENINGOCOCCIC MENINGITIS

Case No.	Age (yrs.)	Sex	Duration of illness at admission (days)	Diagnosis: Symptoms and signs: Drowsiness	Delirium	Coma	Degree of severity*	Spinal fluid: White cell count (× 1000)	Smear	Culture	Blood culture	Treatment: Total dose (gm.)	Duration	Av. blood levels mg./100 cc.: Free	Total	Course (days after beginning treatment): Temperature normal	Clinical improvement	Apparent complete recovery
1	24	F	7	0	0	0	+	41.0	+	0	n†	27	11	6	9	4	2	11
2	27	F	1	0	+	+	+++	57.0	+	0	0	21	10	5	6	4	4	11
3	40	M	3	0	0	0	+	18.0	+	0	0	26	9	6	9	2	2	5
4	49	F	30 hrs.	+	0	0	++	0.06	+	+	0	30	11	5	7	2	2	7
5	16	M	2	+	0	0	++	4.7	+	0	0	18	6	6	7	5	2	7
6	13	F	1	+	0	0	+	8.7	+	0	n	17	6	8	9	8	3	7
7	45	M	1	0	0	0	+	7.8	+	n	n	31	10	3	5	6	2	10
8	63	F	1	+	+	+	+++	1.7	+	+	+	40	14	10	14	12	9	12
9	20	F	1	+	+	0	+++	15.0	+	+	0	26	8	8	10	4	2	7
10	37	M	1	+	+	0	+++	2.5	+	+	0	19	6	7	9	7	2	7
11	25	M	1	+	0	0	+	2.5	0	+	n	33	11	9	11	7	2	7
12	38	M	2	+	0	0	++	53.7	0	+	0	31	10	8	10	Afebrile	2	11
13	18	M	1	0	0	0	++	7.0	+	+	+	21	8	5	7	6	2	9
14	15	F	4	0	0	0	+	10.5	+	0	n	28	10	8	11	8	3	12
15	51	M	5	+	+	0	++	2.4	+	0	0	22	8	7	9	4	2	10
16	15	F	3	+	0	0	+	14.0	+	+	+	21	7	12	14	6	2	8
17	15	M	1	+	+	0	++	3.6	+	0	0	20	7	8	10	13	3	14
18	15	F	2	+	+	+	+++	53.0	+	+	0	22	6	10	11	5	2	7
19	18	M	1	0	0	+	+++	5.6	+	+	n	23	9	5	8	4	2	9
20	36	F	1	+	+	0	+++	112.0	+	0	0	25	9	5	7	7	2	9
21	36	M	1	+	+	0	++	1.6	+	+	0	23	9	6	8	5	4	8
22	65	F	1	+	0	0	++	1.1	+	0	+	25	9	8	10	3	3	8
23	16	M	2	+	+	0	+++	34.7	+	+	n	23	7	4	6	4	3	10
24	23	M	1½	0	0	0	+	6.0	0	+	0	23	7	8	10	4	2	8
25	17	M	1	+	0	0	++	7.8	+	0	0	28	10	11	13	2	2	10
26	19	F	1	+	0	0	++	21.7	+	+	0	22	8	5	7	6	2	8
27	17	M	4	+	+	+	+++	Loaded	+	+	n	23	7	7	9	8	4	20
28	30	M	2	+	0	+	+++	17.0	+	0	+	35	9	9	11	9	3	9
29	27	F	2	+	+	+	+++	3.7	+	+	+	20	7	7	9	7	2	10
30	37	F	3	+	0	+	+++	100.0	+	+	0	25	9	3	4	10	4	14
31	25	F	7	0	+	0	++	7.2	+	+	0	20	7	6	8	5	2	7
32	20	M	12 hr.	+	0	+	++	4.0	+	+	0	23	8	8	10	6	3	8
33	19	M	1	+	0	0	++	8.0	+	+	0	20	7	5	7	3	3	7
34	50	M	2	0	+	0	++	9.0	+	+	n	22	7	12	13	5	2	8
35	18	F	1	0	+	0	++	8.2	+	+	0	23	8	6	7	8	2	10
36	16	M	2	+	+	+	+++	Loaded	+	+	0	21	7	5	7	8	3	10
37	17	F	3	+	+	0	++	Loaded	0	+	0	25	9	10	12	9	2	10
38	29	M	2	+	+	0	++	1.9	+	+	0	21	7	8	10	8	3	8
39	32	M	2	+	+	+	+++	Loaded	+	+	+	40	11	7	9	8	2	10
40	23	F	7	0	0	0	++	2.7	+	0	0	34	12	8	10	5	4	12
41	31	M	3	0	0	0	+	0	0	+	0	20	8	n	n	Afebrile	2	2
42	5	F	?	0	0	0	+	11.6	0	+	+	10.5	7	4	n	2	2	5
43	2½	M	3	0	+	0	+++	6.3	+	0	n	30.5	11	8	11	13	2	14
44	11	M	1	0	+	0	++	5.8	+	n	n	20.5	6	14	17	6	3	8
45	9	M	2	0	0	0	+	3.6	+	0	n	19.5	8	7	9	8	3	8
46	1	M	3	+	0	0	+	0.3	+	+	n	8.5	9	8	10	2	2	7
47	11	F	2	0	+	0	++	48.5	+	+	0	20	7	9	11	4	2	7
48	4	F	1	0	+	+	+++	16.7	+	+	+	10	8	11	15	3	2	7
49	2	F	5	+	0	+	+++	15.0	+	+	+	18	11	8	10	7	4	12
50	22 mos.	M	1	0	0	+	++	8.0	+	+	n	16.5	10	10	12	12	2	8
51	3	F	2	+	0	0	++	7.2	+	+	n	11.5	8	12	14	6	2	7
52	7	F	1	+	+	+	+++	9.7	+	+	n	21	8	12	14	4	3	7
53	1½	M	1	+	0	0	++	Loaded	+	+	0	14	10	6	9	5	2	5
54	12	F	1	+	0	+	+++	80.0	+	+	+	19	6	10	12	7	3	8
55	4	F	28 hr.	+	+	0	++	7.2	+	0	0	10	7	12	14	5	2	7
56	11	M	36 hr.	0	0	0	+	7.5	+	+	0	20.5	7	6	8	2	2	7

* + = mild. ++ = moderate. +++ = marked.
† n = none taken.

the sodium salt of the drug intravenously, in doses varying from 2 to 5 gm. A maintenance dose of 1 gm. was given intravenously every 8 hours thereafter, until the patient was able to receive oral medication. Twenty-eight patients (50%) received intravenous sodium sulfamerazine. Fifteen received only the initial dose intravenously. Six patients required intravenous therapy only during the first 24 hours. In 7 the intravenous administration of sulfamerazine was necessary for periods ranging from 2 to 8 days.

Treatment was continued until the patient had made a clinical recovery. The average duration of treatment was 8.4 days. The shortest period of treatment was 6 days, and the longest 14 days. Thirty-three of the patients (59%) received the drug for 8 days or less. The average total dose of drug for the adults was 24.8 gm., with a range of 17 to 40 gm. For children, the average total dose was 16.6 gm. (range of 8.5 to 30.5 gm.).

So far as possible, daily determinations of the whole blood concentration of both the free and total drug were made in all patients. For adults, the average concentration of free drug on the dosage schedule of 3 gm. per day ranged from 3 to 14 mg. per 100 cc., and the average concentration of total drug from 4 to 17 mg. In children, higher levels of both free and total drug were obtained more readily than in adults. Seven children had average levels of free drug of 10 mg. per 100 cc. or more. Only 4 had average levels of less than 8 mg. Only 6 adult patients had average levels of free drug of 10 mg. or over; 17, however, had average levels of total drug of 10 mg. or more.

In all cases, a diagnostic lumbar puncture was performed immediately on admission to the hospital. A second lumbar puncture was performed in most cases on the 7th or 8th hospital day as a guide to the discontinuance of drug therapy. No other lumbar punctures were performed unless signs of increasing intracranial pressure, failure of clinical response, or suspicion of a developing complication made examination of the spinal fluid advisable. In 6 patients who had lumbar punctures during the course of therapy, the concentration of free drug in the spinal fluid ranged from 2 to 5 mg. per 100 cc.

Fluids were administered liberally. The daily intake in most cases was 2000 to 3000 cc. An effort was made to maintain a urinary output of at least 1500 cc. daily. In children, the fluid intake was governed by age and size. Alkali therapy was not used. Sedation, preferably with paraldehyde, and restraints, when necessary to facilitate nursing, were used as adjuncts to sulfamerazine. An occasional patient was given codeine or aspirin for the control of headache.

One patient (Case 2), a 27 year old woman, received 45 cc. of antimeningococcus serum intravenously on the 3rd hospital day, because of failure to respond rapidly to sulfamerazine. No other patients in this group received antiserum. No other sulfonamide was given to any of these patients, with the following exceptions: One patient (Case 10) received an unknown amount of sulfathiazole a few hours before admission to the hospital; 4 patients (Cases 5, 15, 46 and 50) received sulfadiazine in amounts ranging from 0.3 to 3 gm. prior to admission; 1 (Case 55) received 2 gm. of sulfanilamide intramuscularly prior to admission; 1 (Case 44) received a total of 5 gm. of sulfadiazine on the 2nd and 3rd hospital days. In this case, sulfadiazine constituted one-quarter of the total amount of drug (20.5 gm.) received while in the hospital.

Results of Treatment. During the period of study, all patients who were admitted with the diagnosis of meningococcic meningitis were given sulfamerazine if there was no history of their having received other sulfonamide therapy before entry. In the few cases mentioned in the preceding section, the history of previous sulfonamide therapy

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was not obtained at the time of admission. Patients who were known to have received sulfonamides previous to their admission were treated with sulfadiazine. No other selection of cases was made. In this series of 56 patients with meningococcic meningitis treated with sulfamerazine, there were no fatalities.

In 35 patients (62%) definite clinical improvement, usually manifested by a return of consciousness and mental clarity, was apparent within 24 to 48 hours after admission. All but 1 patient showed improvement by the 4th hospital day. One patient remained in coma with an irregular temperature for 8 days despite adequate therapy. She roused suddenly from the coma on the 9th hospital day, and maintained an uncomplicated course thereafter. Fever tended to persist for several days after definite clinical improvement had occurred. The average duration of fever was 6 days. One patient remained febrile for 13 days, and 2 patients were afebrile throughout the course of their illness.

Complications were observed in 8 patients (14%). Arthritis was present in 1 patient (Case 14) at admission, and 2 others (Cases 10 and 43) developed acute arthritis on the 8th and 9th hospital days, respectively. Three patients (Cases 8, 18 and 27) developed facial palsies during the course of treatment. One of these (Case 27) had bilateral involvement. Diplopia was experienced by 1 patient (Case 35) following return to consciousness. The patient in Case 23 was found to have bilateral nerve deafness on the 3rd hospital day. This complication had been suspected before treatment was begun, but could not be proved until the patient had become rational. The facial palsies were improved before the hospital stay was completed. The nerve deafness persisted. The other complications were transient and had disappeared before the patients left the hospital.

TABLE 2.—TOXIC REACTIONS SHOWN BY 22 OF 56 PATIENTS WITH MENINGOCOCCIC MENINGITIS TREATED WITH SULFAMERAZINE

Toxic reaction	No.	%
Nausea and vomiting	3	5.5
Fever	3	5.5
Simple crystalluria	6	10.9
Crystalluria with microscopic hematuria	2	3.6
Microscopic hematuria (without crystalluria)	2	3.6
Gross hematuria	1	1.8
Renal colic	1	1.8
Leukopenia (below 5000)	8	14.5
Granulopenia (below 50%)	2	3.6

Toxic Reactions. Toxic reactions attributable to the drug were observed in 22 patients (39%) (Table 2). Several showed more than one toxic reaction, but in only 1 case was there a serious complication following the use of the drug. Three patients (Cases 2, 23 and 54) developed nausea and vomiting on the 6th day of treatment after doses of 14, 17 and 19 gm. of sulfamerazine, respectively. These symptoms disappeared 3 days after the cessation of therapy. Three patients (Cases 11, 46 and 50) had febrile reactions on the 11th, 9th and 8th days of treatment, respectively.

Crystalluria was a frequent finding, but was not usually associated with hematuria. Eight patients (Cases 19, 23, 30, 35, 36, 43, 47 and 53) developed crystalluria. Of these, Cases 30 and 36 had urine outputs ranging from 1600 to 1800 cc. The remaining cases had outputs of less than 1000 cc. and the crystalluria cleared when the output was increased. Two (Cases 19 and 43) had microscopic hematuria associated with crystalluria, and 2 (Cases 2 and 6) had microscopic hematuria without demonstrable crystalluria. One patient (Case 9) had gross hematuria with renal colic on the 8th day of treatment after receiving 26 gm. of sulfamerazine. The onset of pain in the right flank was sudden. The pain became almost intolerable within 6 hours after it first appeared. A régime of parenteral fluids and sedation was instituted, with complete relief of symptoms in 12 hours.

Eight patients (Cases 1, 9, 16, 17, 18, 20, 25 and 44) while receiving sulfamerazine developed leukopenia. In no case was the decrease in the white cell count sufficiently marked to warrant cessation of the drug. In several patients the count returned to normal before therapy was discontinued. Two of these (Cases 20 and 25) developed a mild granulopenia. Rapid return of the granulocyte count to normal occurred after sulfamerazine was discontinued. There were no cases in this group of drug rash or of toxic symptoms referable to the central nervous system.

Discussion. The results obtained in this series indicate that sulfamerazine is an effective therapeutic agent in the treatment of meningococcic meningitis. The mortality rate in patients treated with antiserum in the 6 year period 1930–1935 in the Haynes Memorial Hospital was 38%. From 1936 to 1940, a 5 year period in which antiserum and sulfonamide therapy were combined, the mortality rate was 45.7%. Part of this high mortality was probably due to the number of cases received from a severe institutional epidemic. In 1941, when various sulfonamides were used and antiserum was occasionally given, the mortality rate was 12.5%.

During 1942 and 1943, sulfadiazine and sulfamerazine were employed exclusively. There were 52 cases of meningococcic meningitis treated with sulfadiazine during this period. Some of these cases, as explained above, were treated concomitantly with those receiving sulfamerazine. Four patients died, a mortality rate in this group of 7.6%. One was moribund on admission and died 3 hours later. Autopsy showed massive hemorrhages into the adrenal glands. Two others died from causes unrelated to the meningitis after they had made a complete clinical and bacteriologic recovery. Only 1 patient, a 53 year old man, failed to respond to adequate chemotherapy, death occurring 27 hours after admission. Excluding all but this last case, the mortality rate in the group of sulfadiazine-treated patients was 1.9%. As already stated, no deaths occurred in the 56 patients treated with sulfamerazine.*

There was no significant difference in the rapidity of the clinical

* Since this study was completed, 3 patients who were treated with sulfamerazine have died. Two of these deaths occurred within 9 hours after the beginning of treatment.

improvement between the patients treated with sulfadiazine and those treated with sulfamerazine. Complications were observed in 15% of the sulfadiazine-treated cases and in 14% of the sulfamerazine-treated cases. The complications were similar in type and course. Toxic reactions to the drug appeared somewhat more frequently in the sulfadiazine-treated cases, 54% showing some toxic response. In general, however, we believe that the incidence of toxic reactions to sulfamerazine differs little from that observed with sulfadiazine.

Summary and Conclusions. 1. Fifty-six patients with meningococcic meningitis were treated with sulfamerazine.

2. No deaths occurred.

3. Complications of the disease were observed in 8 cases. Except for 1 case of nerve deafness, the complications had cleared before the patients were discharged from the hospital.

4. Except for 1 patient who experienced renal colic, no serious toxic reactions to sulfamerazine were encountered.

5. Sulfamerazine is an effective agent in the treatment of meningococcic meningitis.

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THE "MEGA" SYNDROMES

The Common Relation of the Various Manifestations to the Autonomic Nervous System

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There is a group of anatomic abnormalities in the alimentary and urologic tracts and in the cerebral ventricular system which, because of their diverse clinical symptomatologies and manifestations, have been regarded by most clinical observers as distinct entities apart

from one another. A consideration of their mechanism leads one to correlate all of them in a single inclusive group under the generic term of the "mega" abnormalities.

Idiopathic Dilatation of the Esophagus. Mega-esophagus. Cardiospasm. Idiopathic dilatation of the esophagus is a very rare affliction and is commonly integrated with some form of cardiospam. Alvarez[2] found 34 undoubted instances of this abnormality in the records of the Peter Bent Brigham Hospital—an incidence of 1 in approximately 26,000 patients. Modern esophagoscopists have abandoned the old assumption of the presence of some form of obstructive cardiospasm as the cause of the condition as originally suggested by von Mickulicz[46] in 1882. Instead they integrate this unusual abnormality with a neurogenic incoördination between the lower esophagus and the cardia based upon anatomic or functional disturbances in the autonomic nervous system. This seems to be borne out by the histologic studies of the English school, confirmed by Lendrum[25] in this country, which have demonstrated a disintegration of Auerbach's plexus in the dilated portion of the esophagus. This is now generally accepted as the cause of the trouble. This is also corroborated by Knight's[23] work in cats in which he was able to produce experimentally the radiographic appearance of cardiospasm by cutting the vagi to the lower esophagus. Then he was able to overcome the condition by destroying the sympathetic supply through removal of the celiac ganglion. His work frequently is cited now in support of a pathologic disturbance of the autonomic nervous system. However, because this work was not corroborated in dogs by Cannon[9] and by Vinson, Craig and Moersch,[47] it has been suggested that the changes in Auerbach's plexus follow the dilatation and stagnation of food rather than act as a cause. However, this assumption seems very illogical to me.

The observable phenomena have been studied roentgengologically by Templeton and Moore.[43] In the normal esophagus they describe 3 types of muscular action: (1) a primary wave, a part of deglutition, beginning in the pharynx and traveling down the esophagus; (2) a secondary wave, progressing along the lower half of the esophagus, and (3) a localized contraction which was not peristaltic in character. The lower half of the esophagus undergoes simultaneous contraction, which varies in degree.

In cardiospasm the primary wave, instead of proceeding to the stomach, faded out at the suprasternal notch. In the lower esophagus, peculiar, purposeless, shallow, segmental contractions constantly appeared and reappeared at different levels but strong enough to move the bolus along. They were often accompanied by generalized tonic contractions, which diffusely narrowed the esophageal lumen.

In 3 pathologic specimens, only focal thickening of the muscle fibers was encountered.

While most of the hypotheses implicate an abnormality of the autonomic nervous system, either of pure physiologic function or as the result of organic changes in the sympathetic plexuses of Auerbach, Moschcowitz[30] believes that the probability is strong that this is a

mechanism and not a cause. In any event the end result is the same. The question is raised that the organic degenerative changes witnessed in the Auerbach plexus are not primary but secondary to the ever-present inflammatory changes involving the coats of the esophagus in prolonged cardiospasm. In recent years, evidence has accumulated, according to Moschcowitz,[30] that primary cardiospasm is psychogenic in origin based upon alterations in the cortex of the brain.

Recently Etzel[14] reported that the disease occurs with great frequency among the poor country people of Brazil. Because of their limited dietary, he believes an inadequate supply of vitamin B_1 may be responsible for the degenerative changes in the intramural portion of the autonomic nervous system. Intensive therapy with the vitamin B complex in the experience of Emery,[11] has failed to relieve the condition, so it might seem that if vitamin deficiency is responsible for the nervous disorder, the changes are irreversible.

The case of mega-esophagus reported by Joreg, Borda and Mealla[21] occurred in a 56 year old man in whom there were dermatalogic evidences of pellagra.

Gastric Dilatation. Megastomach. It is common knowledge that in a certain class of individuals there occurs extraordinary accumulations of gastric fluid secretion with associated dilatation of the stomach, frequently to very large proportions. There does not seem to be any particular interference with the motor activity of the stomach; the contractions are normally strong, but always the passage of a stomach tube shows the presence of large quantities of gastric fluid. Commonly this is known as "gastric succorrhea."

I do not include here any deviation of the secretory function from the normal which is associated with visible and demonstrable gross lesions of the stomach such as ulcer, carcinoma, etc.

Curiously enough, this occurs most frequently in the female subject and in those in whom there are always elicitable evidences of functional neurologic activity indicating an unstable and easily irritated and disarranged nervous system.

Hypersecretion has been found in cases of chronic appendicitis, and/or in other apparently unrelated forms of intraäbdominal pathology. According to Alvarez,[3] it has been observed in cases of toxic goiter and in other neurogenic disease. In other instances, it is said to be due to stimuli coming down the vagus nerves.

Pyloric Hypertrophy. Dilated stomachs of this kind in adults are sometimes associated with pyloric hypertrophy in the absence of any inflammatory, luetic, tuberculous or neoplastic lesion. The hypertrophy is centered only in the pyloric muscle.

In infantile pyloric stenosis, the *symptomatology* is of an acute nature and is highly dangerous to life. If no relief quickly follows medical care, the abnormality is corrected by operative division of the pyloric sphincter. This relieves the condition, and follow-up studies indicate the permanence of the relief. I do not know of any instances in which the mega type of stomach has followed.

Saverese[40] describes the thickening as extensive, grossly visible

and palpable, and involving the entire pyloroduodenal tract. The swelling appears to have a smooth surface; its consistency is hard and fibrous; and it is movable to the normal range of mobility of the pylorus. In less severe lesions the pylorus does not show any external evidence of an anatomic change.

On sectioning, the pyloric wall appears greatly thickened and the thickening involves chiefly the muscular layer of the wall. Microscopic studies by Saverese[40] show that the inner circular layer of the tunica muscularis is involved especially. The muscle cells are found to be normal as to their arrangement, form, and size. The connective tissue stroma as well as the subserosa and serosa are always found to be normal. Sometimes there is found in the mucosa a leukocytic infiltration which extends also into the muscularis mucosæ and sometimes also into the submucosa.

The various theories to account for this abnormality include: (1) a congenital origin; (2) a spasmogenic origin, and (3) some combination of the two. In any case, the origin seems to be neurogenic.

According to Jordan and Lahey,[20] "The pylorus is notoriously a prominent effector zone for impulses arising from the hypothalamus, its contraction reflecting nervous states and emotional traumas. This is frequently demonstrated by the symptoms of pylorospasm: 'the lump in the stomach,' nausea and vomiting. When the constriction is sufficiently great and enduring, it may be habitual and result in symptoms which simulate ulcer or neoplasm and findings in the roentgenogram which are often indistinguishable from those of an organic lesion."

Megacolon. The manifestations of the congenital form of megacolon (Hirschsprung's disease) are so well known as not to need repetition. Suffice it to say that the patient is usually a large-bellied, otherwise stunted child, in whom an enormous dilatation of the colon is easily demonstrable. The congenital form is characterized by the impossibility of demonstrating grossly any actual or relative obstructing lesion in the terminal segment, either at the point of junction of sigmoid and rectum, or at the anus. The clinical history, any operatively obtained facts, the termination, and any postmortem findings are sufficiently well known to need no repetition here.

Many cases are reported in later life which are classified as megacolonic, but it appears from the given description that most of these do not belong to the "mega" syndrome. They seem to be unusual exaggerations of the ordinary forms of chronic dilatation of the large intestine proximal to a definitely obstructing lesion, usually a carcinoma. These should be excluded from this discussion. Two of Rankin's[37] cases, reported in 1929, are of this type. His third case is similar, except that here a right colostomy had been present for 2 years.

In Stone's[42] first case the condition was associated with, or followed an imperforate anus at birth.

In Stone's[42] second case an old man had an excessively redundant

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sigmoid, for which no cause could be ascertained. This man had no great symptoms and no surgery was recommended.

A very different state of affairs existed in the following:

Report of a Case. In March, 1926 this patient, then in the fourth decade of life, had a resection of the sigmoid done. In April, 1928 a resection of the middle portion of the rectum was done. In January, 1929 an ileocecal resection was done. Each resection was done in continuity with immediate restoration of the continuity of the bowel by end-to-end suture. Each resection was done for carcinoma. All of the tumors were histologically similar adenocarcinomata; each tumor had the gross appearance of a primary intestinal growth of this type; and in each there was no macroscopic or microscopic neoplastic glandular involvement, although enlarged glands due to inflammatory change were present. After each of the operations, there was an uneventful convalescence with very prompt healing and with a minimum of hospitalization.

Between each of these episodes, the man was in apparently good health and there were little or no symptoms. The rectal tumor was discovered as a non-symptomatic affair during the course of 1 of his regular follow-up visits. The ileocecal tumor caused a moderate amount of discomfort, which called attention to this part of the intestinal tract. Since 1929, the patient was followed regularly. His general health was excellent and his body functions were carried out in the most normal way and without symptoms or discomfort. This was especially true as far as the intestinal functions were concerned.

In June, 1942 he developed some indefinite abdominal complaints. The physical examination revealed no intraäbdominal abnormality and a gastrointestinal series was to all intents normal.

In February, 1943 the patient, while vacationing in Florida, began to complain of increasing abdominal cramps, constipation, nausea, vomiting, and enlargement of the abdomen. The local physician assumed that a mechanical ileus was present and, in view of the history, took it for granted that it was due to a recurrence of the previous malignancy. In the first week of March, when an immediate operation was proposed, because the symptoms, signs, and general physical deterioration of the patient had advanced considerably, the patient left and returned to the city.

When admitted to the hospital on March 11, 1943 the general condition of the patient was still fairly good. He was very much emaciated (probably due to lack of food and to vomiting). The abdomen was distended and a very large loop of gut could be distinguished in the left side of the abdomen. The rectal examination showed a moderate amount of rigidity in the pelvic floor but no malignancy could be distinguished. The rectum was full of feces in spite of the fact, according to the patient's statement, that his bowels had moved daily and that he had passed flatus fairly freely.

Roentgenographic examination (Borrelli) showed an enormously distended colon extending backwards to the ileocolic junction filled with fecal matter admixed with gas.

The picture seemed that of some form of megacolon and it was decided to follow a conservative form of treatment. Following a high compound enema and colonic irrigation, preceded by an injection of prostigmin, a large amount of gas and solid stool was evacuated. This was repeated daily under constant radiographic control with progressively good results both symptomatically and objectively.

By March 15, 1943 the bowel had been completely emptied of stool as was shown in the Roentgen ray observations. An extremely large loop of bowel was now visible in the flat plates occupying the entire left half of the abdomen.

On March 16, 1943 a roentgenographic examination was made by means of a barium enema. This confirmed the previous findings in the flat plates and there was no evidence of any neoplastic growth (Borrelli). This was again confirmed in November, 1943 during one of the follow-up visits.

Uncertainty concerning the etiology and pathogenetic mechanism of megacolon is great and many theories have been advanced for their proper explanation. Alvarez[2] has pointed out that perhaps the simplest explanation of the ordinary form of megacolon is that, in the particular segment of intestine involved in the process, there has been a failure in development of those neurones in Auerbach's plexus, which are in functional and anatomic contact with the intestinal muscle fibers (Nolfe,[31] Alvarez[2,31]).

In the alimentary tract there are 2 sets of plexuses: Auerbach's plexus, which constitutes the peripheral neuron of the parasympathetic system, and is situated between the circular and longitudinal muscular coat; and Meissner's plexus, situated on the inner surface of the circular muscle fibers.

In Auerbach's plexus the fibers of Remak connect the various ganglia and secondary plexuses which are found between the bundles and individual muscle fibers.

Meissner's plexus is formed of small ganglia and their processes form periglandular plexuses and also supply the vascular tissue of the mucosa.

Another type of cell has been described, which is found between the muscle bundles and appears to form some connection between Meissner's and Auerbach's plexuses.

According to Keith,[22] the alimentary canal is physiologically divided into a series of neuromuscular sections, each of which is terminated by a zone of sphincteric activity which blocks the passage of the contraction wave from one section into the next. Each of these sections has a special "pacemaker" center, so that in any given section the passage of any contained material can be halted, and such blockage may spread backwards from section to section.

Keith[22] distinguishes the following sections: (1) a pharyngeal with a sphincter at the upper end of the esophagus; (2) an esophageal extending to the cardiac sphincter; (3) a gastric ending at the pylorus; (4) a duodenal ending at the duodenal-jejunal junction; (5) a jejunal-iliac section ending at the ileocecal valve; (6) a section containing the ascending colon and the proximal part of the transverse colon; (7) the remainder of the transverse descending and pelvic colon down to the rectum. The terminal sphincter is the one at which the intestinal contents are held up normally.

According to Telford and Stopford, the parasympathetic fibers arise from the anterior roots of the sacral nerves and form a trunk which joins the ventral aspect of the superior hypogastric plexus. They describe two bundles which can be traced to a point where they converge to meet and pass to the left side of this plexus. The small trunk can be followed cephalad to the inferior mesenteric plexus, which it joins distal to the origin of the inferior mesenteric artery. This represents the parasympathetic nerve supply to the distal half of the colon. The parasympathetic innervation of the anal sphincters is derived from the pelvic plexus.

At the present writing it seems to be tentatively assumed that the

parasympathetic influence is excitatory to the colonic smooth muscle and inhibitory to the internal anal sphincter, while the sympathetic system transmits inhibitory impulses to the anal sphincter.

Robertson and Kernohan[39] amplified the reports of previous observers in their studies of the plexus of Auerbach in the congenital types of megacolon. They found that the ganglion cells and their connective fibers are definitely smaller than normal; that they were vacuolated; and that the ganglion cells were sometimes absent, or imperfectly formed. On the contrary, in other cases (ulcerative colitis), the ganglion cells and fibers were prominent and even increased in number; and in others (obstructive carcinoma) there were no abnormal changes.

According to Adamson and Aird,[1] the nerves supplying the affected parts of the colon are thicker than normal and the increase is due to a thickening of the epineural tissues rather than to a numerical increase in the contained fibers. That similar connective tissue changes are present in the mesocolon, and in the wall of the bowel, is undoubtedly the expression of secondary effects incident to the chronicity of the abnormality.

The acquired form of megacolon is grossly indistinguishable from the congenital form and here one must sharply differentiate forms of pseudomegacolon. The latter are usually due to obstructing lesions. The former undoubtedly have a similar pathogenetic mechanism as in the true congenital form, even though the primary cause may be entirely different. In the personal case reported here, there is a similar neurogenic mechanism initiated by unavoidable operative division of the same nerve pathways incident to the multiple intestinal resections.

Concomitant and/or Associated Lesions of Megacolon. Many other anatomic aberrations are frequently present in subjects who have congenital megacolon. Excessive elongation of the mesentery (Barth[35]) and various grades of elongation and redundancy of the colon (Pennington,[34] Marfan[35]) have been reported.

Pennington's[34] case included diaphragmatic eventration combined with segmental megacolon and other congenital dystopias.

Segmental neuromuscular defects have been mentioned by Hawkins,[18] Lennander,[35] and by Formad.[35] I wish to speak especially of optic nerve and ocular lesions and of cerebral and ventricular defects.

Associated Neurologic Abnormalities: A. Optic Nerve and Ocular Abnormalities.

Case Reports. Worcester-Drought and Shafar[52] report the following experiences in which megacolon was associated with ocular changes:

1. One case associated with retinitis pigmentosa, optic atrophy, and right cataract.

2. A 38 year old woman with central choroidal excrescences and bilateral scotomata; symptoms since the 24th year; diagnosed as subacute intestinal obstruction and partial volvulus.

3. An 8 month old boy with symptoms since premature birth at 8 months; blind; urinary incontinence; some improvement later; bilateral optic atrophy without any neurologic or muscular manifestations. Cerebrospinal fluid and Wassermann negative.

Worcester-Drought and Shafar[52] cite the following cases from other sources:

4. Wilbuat[51] of Amsterdam: A 17 year old female, disseminated choroiditis; adiposity; enlargement of the sella turcica. Father had similar eye changes.
5. Gurich:[15] Bilateral coloboma of the optic nerve merging with extensive right choroidal coloboma and left total detachment of retina. Other abnormalities included narrow sella turcica; pigeon chest; and mild mental deficiency.

B. Cerebral and Ventricular Abnormalities:

There are instances in the literature in which megacolon has been associated with hydrocephalus. The following are examples:

In one of the cases reported by Worcester-Drought and Shafar[52] there was present a congenital megacolon and a congenital hydrocephalus. No block in the pathways of the cerebrospinal fluid was observed in the encephalograms, the air passing into and filling the ventricular system and being visualized in the subarachnoid space over the cerebral hemispheres.

In a case reported by Watts and Uhle,[50] congenital megacolon was associated with recurrent episodes of Jacksonian epilepsy. Encephalography showed an enlarged ventricular system equal on both sides.

Hydrocephalus. Congenital hydrocephalus is frequently accompanied by other abnormalities of the central nervous system, such as spina bifida, encephalocele, and so on, or by abnormalities elsewhere, *e. g.*, clubfoot, syndactyly, and so on. The anatomic and clinical picture is well known; the widely dilated ventricles containing a liter or more of fluid; the obliteration of sulci and convolutions and the atrophy of the cerebral tissue to a mere thin bag; the corresponding dilatation of the entire ventricular system; and the corresponding changes in the brain case. In the great majority of the cases there is no demonstrable obstruction in any part of the ventricular system.

The combination of hydrocephalus and other congenital abnormalities, both in the central nervous system and elsewhere, is not uncommon. The association with megacolon is striking. The possibility presents itself as to whether the interference with the development of the brain by the expanding ventricular system can in any way be correlated with dysfunction of the autonomic nervous system which appears adequately to account for the megacolon. The site of the disturbance may lie in the peripheral, ganglionic, or central portions of the autonomic nervous system.

The available data are as yet insufficient to say definitely that autonomic elements exist in the cerebral cortex. But various gastrointestinal disturbances preceding, accompanying, or replacing focal epileptic seizures are now thought to emanate from a cortical level (Penfield and Gage, 1933).[33]

Experimentally, Bochefontaine (1876)[8] associated stimulation of the sigmoid gyrus with intestinal movements. The observations were experimentally confirmed by Bechterew and Mislawski (1890);[7] by Beattie and Sheehan (1934);[6] and by Watts and Fulton (1934),[49] who removed the premotor area from the cortex from both hemispheres in the monkey and produced intussusception with fatal intestinal obstruction. This could never be obtained after severance of the vagi. Mettler[28] and his co-workers (1936) removed the frontal lobes bilaterally and caused hyperactivity of the stomach and pyloric spasm, while

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similar disturbances of motility were produced by removal of one or of both cerebral hemispheres.

Morbid hunger has been encountered in cases of cerebral tumor, and Levin (1936)[26] described in a group of children an interesting syndrome consisting of periodic attacks of somnolence and morbid hunger which he considered as possibly being due to a corticothalamic derangement. Previously (1932), Cushing[10] had made the observation that experimental lesions anywhere in the intracranial course of the tracts leading from the anterior hypothalamus to the vagal centers were liable to give rise to ulceration and perforation of the stomach.

It seems, then, that there is considerable evidence to support the existence of cortical and hypothalamic centers which control the activities of the autonomic nervous system. It is conceivable that an embryologic defect, attributable to, or associated with hydrocephalic expansion of the ventricles, might cause changes in these higher centers and secondary effects in the Auerbach plexuses farther down, and consequent derangement of intestinal motility and so result in megacolon. It must be admitted, however, that no definite proof exists at present as to a central origin of Hirschsprung's[19] disease. Further observation is necessary to discover the primary seat of the neurogenic disturbance in congenital megacolon. Nevertheless, the accumulated data is more than suggestive.

The "Mega" Syndrome in the Urologic Tract and Its Association With the "Mega" Syndrome in the Alimentary Tract.—Megacolon is commonly associated with disturbance of bladder function and the latter becomes the prominent feature in many cases.

1. *Chronic Bladder Dilatation—"Mega" Bladder.* The association of unusual and extraordinary dilatation of the bladder has been noted by a number of observers.

Telford[44] stated that he has observed infrequent urination and a huge thin walled bladder in association with megacolon.

Richer's[38] case is a very typical example:

> In a 50 year old woman there was a sudden attack of retention of urine, the bladder reaching to the umbilicus and containing several liters of fluid. Continued catheterization over a period of 1 month was not followed by any improvement. Then attacks of intestinal colic called attention to an enormous coëxisting dilatation of the entire colon.
>
> There were no signs of tabes or other motor or sensory lesion of the central nervous system. The spinal fluid was negative. No cause was found on physical and laboratory examination and on roentgenologic examination by barium enema for the colonic dilatation. No particular effect was observable after treatment. Richer[38] rightly assumed that this was a case of coëxisting "mega" enlargement of both bladder and colon.
>
> Richer[38] mentions another case without giving any details occurring in an 18 year old girl who presented herself because of the presence of a megacolon and in whom there was also present "considerable retention of urine."

Cases have been referred to by other observers. In these typical cases the only abnormality of the bladder is its unusual size, permitting remarkably infrequent urination with the voiding of large quantities at one act.

In none of these cases can the condition be regarded as atony of the bladder, since in all the detrusor muscle was capable of powerful contraction. It seems that there is dysfunction in the vegetative nervous supply of the bladder.

The nerve supply of the bladder includes: (*a*) the sympathetic system (chiefly the presacral nerves); (*b*) the parasympathetic system (the pelvic nerves), and (*c*) the pudic nerves.

The pudic nerves are thought to be of somatic origin, but they may possibly transmit also impulses of involuntary type, although this is ordinarily the function of the autonomic nerves.

All three of these sets of nerves contain both afferent and efferent fibers.

The modern conception of the innervation of the bladder contains both anatomic and physiologic observations and is based on the work of Learmonth.[24] Simons and Emanuel[41] accept the imbalance idea of the innervation of the bladder until it is thoroughly disproved and they feel that there is much in the researches of Barrington[4] to substantiate this stand. The imbalance theory of bladder innervation is that the sympathetic and the parasympathetic distribution of the thoracicolumbar and sacral outflows to the bladder are antagonistic and balance each other to a certain extent.

The general plan of the autonomic supply to the bladder is very similar to that in the colon. The parasympathetic branch carries contracting or emptying stimuli, while the sympathetic branch controls the bladder sphincter.

Both Watkins,[48] Entz, and Haymond[12] express the opinion that the nature of this bladder abnormality suggests strongly that it is analogous to and is the nearest counterpart to congenital megacolon.

2. *Megalo-ureter.* This bladder abnormality (megalobladder) may exist alone or it may be associated with similar general dilatation of the ureter (megalo-ureter) and kidney pelvis (megalopelvis). There are fairly numerous examples in the literature and in one's practice. I do not refer to solitary or multiple cysts of the kidney, which specimens exhibit a lining membrane, and are within the kidney substance. They are not connected with the urinary excretory tract, but in all cases there is also evidence of embryonal developmental changes in the kidney parenchyma. I do not refer to various forms of dilatation at the lower end of the ureter, usually included under the terminology of "ureterocele." These, too, nevertheless, are most commonly of congenital origin.

According to Morison,[29] localized spasms occur in the ureter which are usually intermittent in character. The spasms occur either in the entire extent of the ureter or they are restricted to certain zones in which there is normally a physiologic narrowing (pelvo-ureteral zone, the crossing of the common iliac vessels, the zone of the broad ligament in the female or of the vas in the male, and the transmural zone). The spasms give rise to pain which is referred to definite areas of the abdomen. In long-standing cases, submucous and interstitial changes follow. To my mind, these spasms seem to correspond to pyloric

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spasms, or to spasms which are frequently seen in various corresponding strategical zones of the large intestine. It seems most likely that all of these forms of spasms have a common neurogenic origin.

3. *Megalopelvis* (*Hydronephrosis*). Latent hydronephrotic distention of the kidney, without apparent clinical signs, occurs in 50% of the cases, and is revealed only by some complication or by various bizarre clinical syndromes, which can be classified as follows:

1. Chronic syndrome: (*a*) a dyspeptic form which simulates gastric or pyloric tumor; (*b*) an enteritic form which simulates mucomembranous enteritis, and (*c*) a form of "chronic appendicitis" which is encountered most frequently.

2. Acute abdominal syndromes in which the hydronephrosis can simulate intestinal occlusion or peritonitis.

It is interesting to list the "intrinsic" causes which are assumed to precede these renal urologic dilatations. I am indebted to Mathé[27] for this very complete classification:

1. *Congenital:*
   - (*a*) Congenital *per se*.
   - (*b*) Associated with the following anomalies of the kidney and ureter:
     - (1) Bifid pelvis and ureter
     - (2) Double pelvis and ureter
     - (3) Abnormal insertion of the ureter
     - (4) Horseshoe kidney
     - (5) Ectopic kidney
     - (6) Fused kidney
     - (7) Abnormal outlet of the ureter
     - (8) Aberrant distribution of the blood-vessels
     - (9) Stricture of the valve formation at the ureteropelvic junction
2. *Acquired:*
   - (*a*) Renal ptosis associated with obstructive bands, kinked ureter, and aberrant vessels
   - (*b*) Lithiasis
   - (*c*) Renal torsion
   - (*d*) Stricture of the ureteropelvic junction
   - (*e*) Stricutre of valve at the ureteropelvic junction
   - (*f*) Tuberculosis
   - (*g*) Tumors of the cortex, pelvis, and ureter
   - (*h*) Aneurysm of the renal artery
   - (*i*) Pyelonephritis
   - (*j*) Interstitial nephritis
   - (*k*) Neurogenetic causes; neuromuscular dysfunction, and sympathicotonia
3. *Traumatic:*
   - (*a*) Late sequel of trauma to the cortex, pelvis, or upper ureter
   - (*b*) Following surgical interventions
     - (1) Pyelotomy
     - (2) Ureterotomy
     - (3) Ureterostomy
     - (4) Surgical injuries to the ureter itself due to cutting, clamping, or tying of the ureter during operation on other organs.

Considering the "intrinsic" cases of hydronephrosis, one group of investigators thinks that the greater majority of causes are obstructive phenomena. I am, personally, in complete agreement with the opposing group who believe that numerous cases of hydronephrosis

(megalopelvis) are congenital in nature. Bazy[5] was the first to insist on the congenital nature of hydronephrosis (megalopelvis—Bazy's disease), pointing out the fact that megalopelvis and megaloureter often exist since birth and are often associated with megalocolon, diverticula of the esophagus, etc. The opinion (Papin,[32] Mathé[27] *et al.*) is gaining ground that this congenital anomaly (megalopelvis) occurs much more frequently than was previously supposed or realized; that it exists at, and develops progressively from birth onwards, both because of the original anomaly and because of other subsequently appearing factors; that stones associated therewith are secondary to preëxisting stasis; that accessory vessels and high insertion of the ureter are without significance and/or result from the pelvic dilatation; and so on. These additional factors occur only when considerable damage has preceded. If we accept this viewpoint, the term hydronephrosis is misleading and should be reserved for other types of renal distention. The term "megalopelvis" seems much more appropriate.

Harrison's[17] cases undoubtedly belong in the congenital group. It is very suggestive that supposed correction of "structural abnormalities" such as "stricture" and "vesical neck obstruction" did not relieve the condition nor influence the final outcome. The causal relation of these anatomic abnormalities must, therefore, be considered questionable.

One of the cases cited by Mathé,[27] of which a photograph is presented, is a typical hydronephrotic distention of the kidney (megalopelvis) in which the kidney tissue has apparently disappeared entirely, and in which a stone is present in a lower pocket. Mathé[27] remarks, that the "stone is secondary to preëxisting stasis rather than being an etiological cause. . . ."

This is a typical example in the experience of almost everyone. I have seen several of such cases in my own practice and in the hospital experience of my colleagues.

The picture is almost always complicated by infection. Other factors then come into play, especially calculus formation, and the clinician usually attributes the pathogenetic mechanism and the resulting clinical picture to the infection as the primary and/or most important cause. This, of course, is an erroneous assumption.

The Relation of the "Mega" Abnormalities to a Neurogenic Pathogenetic Mechanism. In each of these anatomic localizations, the "mega" abnormality, described herein, has this phenomenon in common: that in each an extraordinary accumulation of the normal fluid and/or solid content of each takes place. In each case, the thought usually runs to the relationship of secreting and excreting phenomena, the net disturbance of which results in the extraordinary accumulation and the necessary consequent distention. This thought results in the current conceptions regarding the pathogenetic origin of the disease.

Nevertheless, from the accumulated evidence, it seems that this factor is of little importance in the pathogenesis of the cases in the alimentary tract, and in the megabladder and megalo-ureter cases, but

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is of more importance in the megalopelvis and in the megaventricle (hydrocephalic) cases.

In the alimentary canal, the fibers of the sympathetic system corresponding to the derivatives of Meissner's plexus are known to ramify around the secreting glandular structures in the wall of the viscus. They undoubtedly influence the secretory activity of these glandular cells and the assumption is not far fetched that, in the general disturbance of neurologic function, an increased activity of the secreting mechanism takes place which adds to the general picture. This has special reference to the gastric cases, and possibly to the renal cases.

The thought goes further in considering the sympathetic supply of the appropriate part of the vascular network. Some part of the increased accumulation of fluid might be due to increased blood supply related to extraordinary activity of the nerve plexus and a consequent dilatation of the vascular channels. This activity finds its greatest field, most probably, in hydrocephalic accumulations (increased blood supply and secretion in the ventricular ependyma).

There seems to be much more pathogenetic importance in the neuromuscular dysfunctions of the sympathetic system. In most of the instances this is of congenital origin. In a few cases, it follows trauma (operative or other) in which the same result follows a mechanical (division of nerve paths) interruption of normal nerve impulses.

Neuromuscular dysfunction, so called "sympatheticotonus" occurring in lesions of the autonomic system can cause atonic relaxation of a hollow viscus or dilatation because of any relative obstructing spastic ring muscle. Both pathologic processes result in dilatation and finally in an atonic condition.

Atony of a hollow viscus is never primary. It is caused either by abnormal innervation, by obstruction, or by both factors. Continuous intraviscus retention from any cause will produce atony of the muscular wall. In some cases it is difficult to determine which factor is primary. With most cases, atony and obstruction are inextricably combined; and in muscular lined viscera, a certain amount of hypertrophy precedes the final relaxation. In a parenchymatous organ (kidney, brain), atrophy follows with disappearance of the cellular elements.

Irritation or paralysis of the sympathetic splanchnic or pelvic ganglions, and so on, can cause atonic changes in the kidney pelvis (Mathé);[27] in the ring muscle of the ureteropelvic junction (von Lichtenberg), and in the major and minor renal calyces, in the lower esophagus and cardia (Alvarez,[2,3] Lendrum,[25] Knight[23]) and at the pylorus (Alvarez,[2,3] Saverese).[40] This results from overstimulation of the sympathetic nerves (Harris and Harris);[16] or, as other evidence seems to show, rather from an uncoördinated and badly integrated action between the opposing activities in the sympathetic system of nerves.

The factors involving sphincteric dysfunction in a hollow organ are: (1) imbalance of innervation, with predominance of the sympathetic or filling nerves; (2) rigidity or failure of adequate relaxation of the internal sphincter referred to as dysectasia; (3) apparent failure of coördination of segmental reflexes involved in the normal act of empty-

ing of the viscus referred to as achalasia; and/or (4) a disturbance of the suprasegmental or cerebro-spinal reflex.

There is evidence to make one believe that functionally and mechanically the root of the difficulty is failure of time correspondence and coördination between an approaching contraction wave and relaxation of the sphincter fibers at one or more of the strategic points. Hurst has invented the term "achalasia" for this functional incoördination with special reference to the pyloric sphincter. The adult variety of acquired megacolon is explained in this way by Etzel,[13] and he points out that the case of mega-esophagus and of otherwise unexplainable extraordinary forms of gastric dilatation owe their production to this mechanism. Etzel[13] also integrates this functional disturbance with destruction or malformation of Auerbach's plexus.

The sphincters are normally in a state of normal contraction, and sympatheticotonus makes their relaxation difficult, thereby setting up a more or less continual spasm resulting in increased tone of the muscle fibers. This leads to increased intravisceral pressure, dilatation and delayed emptying time with extraordinary intravisceral accumulations with no mechanical obstruction. According to von Lichtenberg,[45] this disorder is by no means rare in the renal cases, making up 59% of 80 cases of hydronephrosis operated by him, and he has often demonstrated this muscular contraction during operation.

While these viewpoints were supplied by Mathé[27] to the urologic mechanism, their applicability to the alimentary canal seems unquestionable to me; and it is most noteworthy that von Lichtenberg[45] compares neuromuscular dysfunction in the urologic apparatus with cardiospasm and pylorospasm for which he assumes a like mechanism.

The conception seems unavoidable that the various observable clinical phenomena of the "mega" syndrome in the different anatomic localizations are, in reality, manifestations of a general disease, the essential basis of which is a neuropathy of the autonomic nervous system. This finds its inception most commonly in congenital abnormalities of physiologic function or structure and are followed subsequently, as the disease continues, by more pronounced or newly developed anatomic changes of definite character.

In other cases, the phenomena appear in early adult life and continue. It seems that in these there are abundant evidences of instability of nervous functional activity, in which irritability and emotional outbursts are characteristic. These cases occur most commonly with the lower esophagus and cardia cases and with the pyloric cases. This group has important relationships with psychosomatic medicine, a clinical segregation which is increasing in extent as our knowledge of this comparatively new branch of medicine accumulates.

In other cases of non-congenital origin, this form of neuromuscular dysfunction or incoördination or both, sometimes follows trauma. The personal case described above belongs in this category inasmuch as the condition followed operative trauma. In the traumatic cases, the dynamic upset of physiologic function undoubtedly corresponds to mechanical interference with the carriage of nerve impulses or with

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their proper integration in the physiologic purpose by division of nerve pathways. I believe that in these cases there is no relation to obstructive phenomena.

Summary. The alimentary and urologic tracts and the cerebral ventricular system are occasionally the seats of malformations which resemble one another to the extent that a dilatation of the contained cavity occurs, varying from moderate to most extraordinary extent. Commonly there is a single localization of the abnormality. Less commonly several localizations exist either in one or in more than one of these systems. Commonly other congenital defects and deformities coëxist. While this is most often a congenital manifestation and appears at, or can be traced directly to the time of birth from which point it progressively develops, rarely, similar gross anatomic changes are observable later in life which cannot be so integrated, which occur apparently spontaneously in the absence of obstructive phenomena or which follow some operation in which a radical change is unavoidably produced in the normal anatomy (postoperative megacolon cases).

The factor of secretion seems to play either no rôle or at most an indifferently contingent or adjuvant part, or both, in the production of this abnormality in the alimentary and urologic tracts. In both of these localizations the available factural knowledge seems to indicate an exact similarity in the pathogenetic origin and mechanism. This is most commonly a neuromuscular deficiency and dysfunction, characterized by faulty integration of nerve impulses, so that there is incoördination between an approaching contraction wave and the necessary relaxation of a functional or anatomic sphincteric arrangement at a strategic point. Sometimes this is a purely functional disturbance. At other times it is based upon anomalous or deficient anatomic structure centered in the autonomic nervous system, either in the ganglionic cells (Auerbach's plexus) or in their connecting nerve pathways. The cases are of congenital origin, in which instance there are at times some indications of disturbance in the higher autonomic centers. In a few cases there is a traumatic origin and then the mechanism is a local one.

In the hydrocephalic cases (megaventricle) the factor of secretion seems important. When the megaventricle is associated with megacolon, it seems that the atrophic changes in the cerebral cortex involve higher autonomic centers which, in turn, seem to be integrated with changes in the lower autonomic centers (plexus of Auerbach), and the megacolon then follows.

In the lower esophagus, cardia and pyloric cases there is evidence of the presence of unstable nervous functional activity. In some of these there seems to be some connection with psychosomatic medicine. When there is marked gastric succorrhea with the extraordinary gastric dilatation ("mega" stomach), the ramifications of the nerve fibers derived from Meissner's plexuses around the secreting lands in the stomach mucosa seems to indicate a pathogenetic relationship between the two.

While all of these differ markedly in their manifestations in accord-

ance with their localizations and with any added or complicating factors, they show general similarities in the resulting architecture of the affected part. There are frequent neurologic complications. They involve pathogenetically the same part of the nervous system. And they seem to have a similar pathogenetic mechanism. All of the facts lead one to suspect and assume an origin in the autonomic nervous system. It seems appropriate to include them all under the generic term of the "mega" syndrome.

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THE PROTEIN CONTENT OF EDEMA FLUID IN PATIENTS WITH ACUTE GLOMERULONEPHRITIS

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MOST textbooks of medicine state that acute glomerulonephritis is a diffuse disease of the body capillaries and that edema occurs as the result of widespread capillary damage. It is pointed out that the edema fluid in acute nephritis contains a high concentration of protein and that to account for this the capillaries must be injured and abnormally permeable to protein. Examination of the data available in the literature reveals that only a few determinations of the protein content of the edema fluid in acute nephritis have been made and that the methods used are open to criticism. It seemed worth while, therefore, to measure the protein content of edema fluid of additional patients with acute nephritis. If this fluid contained a high concentration of protein it might be assumed that generalized capillary damage was at least in part responsible for the edema. If the protein concentration were low this explanation for the edema would not be tenable.

Methods. Edema fluid was obtained from patients with acute glomerulonephritis by inserting several 23-gauge needles into the subcutaneous tissue of an edematous portion of the body. They were left in place for not more than 5 minutes. From time to time the local tissue pressure was increased by stretching the skin of the part. The needles were removed and the fluid in them collected in fine glass capillary tubes. The size of the sample was obtained from the difference in weight of the filled and empty capillary tube. Only a few milligrams of fluid were necessary for analysis. The fluid was examined under the microscope without removing it from the capillary tube. If it was cloudy, or contained a large number of red blood cells, the specimen was discarded. If there were only a few red cells, the specimen was accepted, because experience showed that the protein concentration of the fluid was not significantly affected by a small number of cells. At the same time blood was obtained for the determination of the total protein nitrogen and nonprotein nitrogen contents of the serum. The total nitrogen content of the edema fluid was determined by a modified micro-Kjeldahl procedure with nesslerization and colorimetric determination by a photoelectric colorimeter.[6]

Results. Determination of the protein content of edema fluid was carried out in 10 patients with acute glomerulonephritis (Table 1). All were children or young adults who developed classical acute nephritis with generalized edema, hypertension, and hematuria. In none was there a history of previous renal disease. In most instances the acute nephritis followed an upper respiratory infection; in 2 patients it occurred as a complication of scarlet fever. In most of the persons studied the onset had been relatively abrupt and was moderately severe. None of the patients died during the acute illness, and in all instances there was almost complete recovery during the period of hospitalization, as evidenced by subsidence of symptoms and disappearance of the urinary abnormalities. During the acute stage of the disease some of the patients had moderate cardiac enlargement and pulmonary congestion, as determined by Roentgen ray examination. There were no complicating diseases which would have been expected to produce a serious alteration in the serum protein level.

TABLE 1.—SUMMARY OF OBSERVATIONS ON SUBCUTANEOUS EDEMA FLUID IN 10 PATIENTS WITH ACUTE GLOMERULONEPHRITIS

	Blood serum		Protein content of edema fluid	
Patient	Non-protein nitrogen, mg. per 100 cc.	Total protein, gm. per 100 cc.	Leg gm. %	Sacral region, gm. %
1	41	5.8	0.4	
2	33	6.5	1.0-1.1	
3	63	6.1	0.2-0.3	0.5-0.7
4	198	6.3	0.1-0.3	
5	34	5.8	...	0.8
6	..	6.5	...	1.0
7	54	5.8	0.1	
8	24	5.2	0.1-0.2	
9	..	6.4	...	0.9-1.0
10	30	4.9	0.3	
Average	..	5.9	0.4	0.8

In 7 patients edema fluid was obtained from subcutaneous tissues of the leg. The average protein content of this fluid was 0.4 gm. % with extremes of 0.1 and 1.1 gm. %. In 4 patients the fluid was from the subcutaneous tissue in the sacral region. The average protein content of this fluid was 0.8 gm. % with variation from 0.5 to 1.0 gm. %. In 5 instances 2 or more samples were obtained from the same patient and in none was the variation in protein content more than 0.2 gm. %. There was no apparent correlation between the serum protein and non-protein nitrogen levels of the blood and the protein content of the edema fluid. The average serum protein concentration in the 10 patients was 5.9 gm. per 100 cc.

Comment. The average value of 0.4 gm. % for the protein content of the edema fluid from the legs of these patients with acute glomerulonephritis is considerably lower than previously recorded. The subcutaneous edema fluid of the legs in patients with cardiac failure contained an average of 0.2 gm. % of protein.[7] Thus, the protein concentration of the edema fluid of the legs in acute nephritis and in cardiac failure showed no significant difference. The protein content of the fluid from the sacral region in the patients with acute nephritis averaged 0.8 gm. %. In patients with cardiac failure who

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had no lowering of the plasma protein concentration, the protein content of the fluid from the subcutaneous tissue of the sacrum averaged 0.6 gm. %.[8] Again there was no significant difference between the protein content of the edema fluid of the sacral region in patients with congestive heart failure and those with acute nephritis.

In acute nephritis, edema is not usually extreme and, in general, the procuring of samples of edema fluid is much more difficult than in conditions where fluid retention is more pronounced. When obtaining fluid for analysis, the needle must not be left in place too long or else local capillary damage will occur, and almost pure blood serum will be obtained. In none of our cases was the needle left in place longer than 5 minutes. As a check on the validity of the method used in such patients with minimal amounts of edema, additional studies were carried out on patients with cardiac failure. Samples of edema fluid were obtained from patients with massive edema. Fluid flowed freely as soon as the needle was inserted. Later, after most of the edema had been reduced by either elevation of the part or diuresis, samples of edema fluid were again obtained. This time fluids had to be forced into the needles by raising the tissue pressure by local pressure. No significant difference was found in the protein content of the fluid under the different conditions.

The condition of the skin and subcutaneous tissues must be known in order to evaluate the significance of a high protein concentration in edema fluid. If the area is inflamed, the edema fluid will always contain considerable protein. It is possible that the protein content of subcutaneous edema fluid in post-scarlatinal nephritis may be higher than in patients who have not had any reaction in the skin. It is of interest that the edema fluid of the leg which had the highest protein content was from a patient with post-scarlatinal nephritis.

Although general statements regarding the protein content of edema fluid in acute nephritis are common, reports of analysis of edema fluid are rare. Beckman[1] studied 4 patients with acute glomerulonephritis. The edema fluid protein content in 3 patients was 1.12, 1.12 and 2.52 gm. per 100 cc., while in the fourth repeated observations ranged from 1.12 to 1.96 gm. per 100 cc. The protein content was determined by a refractometer. Peters and Van Slyke[5] mention 1 case of acute nephritis in which the protein concentration of the edema fluid was 0.1 gm. per 100 cc.

The data presented here are not compatible with the thesis that the edema of acute glomerulonephritis can be differentiated from that of congestive heart failure by study of the protein content of the edema fluid. There seems little reason to believe that the edema is primarily dependent on an increase in capillary permeability. Edema which is caused by a sudden marked increase in capillary permeability should be associated with hemoconcentration. Acute nephritis is not accompanied by hemoconcentration. Indeed, in the cases reported in the literature[4] and in the 2 patients in this series on whom the data were obtained, the hematocrit reading rose as the edema disappeared, indicating that in the edematous state there was hemodilution rather than hemoconcentration. An opportunity to observe the changes in

the hematocrit reading when the capillary permeability is suddenly increased, occurred during the study of a patient with widespread giant urticaria resulting from the previous administration of horse serum. The fluid in urticarial wheals is known to have a high protein content, demonstrating that the capillaries are abnormally permeable to protein. A few hours after the onset of the urticaria the hematocrit reading was 46. Several hours later at the height of the reaction it was 49. Four days later, after the urticaria had subsided, the reading was 36. The edematous state was accompanied by hemoconcentration and hemodilution occurred as the urticaria subsided. This is the reverse of what is observed in acute nephritis.

The simplest explanation for the presence of edema in acute nephritis is that the fluid intake exceeds the fluid loss from the body, because of a disturbance in renal function. The extracellular fluid content of the body is increased and edema results. The retained extracellular fluid is deposited throughout the tissues in areas where the capillary pressure is high or where the tissue pressure is low. When the patient is upright the excess fluid accumulates in the part of the body below the heart, because the capillary pressure there is elevated by the effect of gravity. On lying down, the capillary pressures throughout the body become more nearly equal, the excess fluid reënters the blood stream and is redistributed throughout the body in accordance with the dictates of tissue pressure. Burch[2] has shown that the formation of edema in the tissues usually results in a rapid rise in tissue pressure, with the result that the rate of transudation into the tissues is slowed. The tissues of the eyelids were unusual in that edema formation caused little rise in tissue pressure. When fluid is redistributed with the patient recumbent, the eyelids swell rapidly, because in this area the edema formation is unopposed by a rising tissue pressure.

The thesis that the accumulation of edema about the eyelids at night is caused by the easy distensibility of these tissues, rather than by diffuse capillary damage, is supported by observations on patients with chronic constrictive pericarditis. These patients may become edematous before they have any orthopnea. If they are able to lie flat in bed at night, edema of the eyelids may be present when they awake. During the day, when they are sitting or standing, the edema of the lids disappears and edema of the lower extremities can be detected.

Patients with acute nephritis may develop congestive heart failure. LaDue[3] has shown that in acute nephritis with edema the venous pressure is elevated and the transverse diameter of the heart is increased. He believes that heart failure, with its increased venous pressure, accounts for the edema. Data previously presented from our clinic has shown that in chronic congestive heart failure the retention of salt and water is dependent on a disturbance in renal function secondary to the failure of the heart.[9] The edema fluid would be expected to have the same protein concentration regardless of whether the renal dysfunction is the result of kidney damage from the nephritis or the result of altered renal physiology from heart failure. The degree of changes in the kidney, as seen under the microscope, and the knowl-

edge that retention of fluid may be the cause, rather than the result of the rise in venous pressure,[9] support the thesis that primary renal damage is the chief factor causing salt and water retention. It is difficult to believe that cardiac failure alone is responsible for the striking oliguria seen in certain patients with acute nephritis, though heart failure undoubtedly plays an important rôle in certain instances.

Summary and Conclusions. The protein content of edema fluid in 10 patients with classical acute glomerulonephritis has been determined. In 7 patients in whom edema fluid was obtained from the leg, the average protein content was 0.4 gm. %. In 4 instances, when the fluid was obtained from the sacral region, the average protein content was 0.8 gm. %. These values do not differ significantly from those obtained on the edema fluid of patients with congestive heart failure studied by similar methods.

The evidence at hand indicates that the cause of edema in acute nephritis is water and salt retention secondary to a disturbance in renal function, and not the result of diffuse capillary damage throughout the body. The method of study is not suitable for determining whether the retention of salt and water results from the pathologic process occurring in the kidney or from heart failure, as suggested by LaDue. The extensive pathologic changes seen in the kidney in acute glomerulonephritis support the view that the altered renal function is caused by these pathologic changes, rather than by altered renal physiology because of failure of the heart.

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OBESITY AS A CLINICAL PROBLEM

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Statistics based upon standardized death rates indicate the apparent wisdom of avoiding obesity.[10] The increased mortality rate in the obese group is associated with a higher incidence of cardiovascular

diseases. The present study seeks to define, in part at least, the complications associated with obesity, and to review the experience of a large clinic with attempts at weight reduction. The effect upon hypertension of a change in body weight has been investigated. A search has been made for possible etiologic factors of obesity in disorders of the central nervous system and of the endocrine glands.

Materials. Patients and records of the Metabolism Clinic of the New Haven Hospital have been selected for study. The obese group, 141 in number, consisted of 54 women who weighed 180 to 200 pounds, and 87 patients of both sexes who weighed 200 to 484 pounds. The latter included 62 females and 25 males; 63 of these patients weighed 200 to 250 pounds; 17 were in the 250 to 300 pound group; 7 others weighed between 300 and 484 pounds. A few patients who were large rather than obese were not included in this study. One hundred non-obese patients selected at random from the same clinic served as controls. The population of this clinic includes all diabetics in the entire out-patient department, all patients with known or suspected disorders of the thyroid and other endocrine glands, all cases of glomerulonephritis and many cases with other types of renal disease, and various nutritional disturbances. The last group includes many individuals referred for therapy of obesity and study of possible endocrine factors. It also serves as a follow-up clinic for a portion of the patients with urinary tract infections and for some of the patients with a history of toxemia of pregnancy (Table 1).

TABLE 1.—PRIMARY DIAGNOSIS IN OBESE AND CONTROL SERIES

	Obese	Control
Diabetes	73	61
Obesity	41	
Hyperthyroid	11	14
Myxedema	1	2
Goiter	4	1
Renal disease	3	17
Toxemia	5	3
Hypometabolism	1	1
Hypermetabolism	1	
Basophilism	1	
Steatorrhea		1
Total	141	100

After a preliminary survey certain conditions were selected for detailed study. The presence or absence of diabetes mellitus, varicose veins, gall bladder disorders, joint symptoms, and vascular disease was noted in all subjects. The effects of weight change on hypertension could be analyzed in 41 of the patients in the obese group. The records of attempts at therapeutic reduction were adequate in 67 subjects over a sufficiently long period to permit some judgment of the results.

Criteria for Symptoms and Diseases. The diagnosis of diabetes mellitus was based on the usual criteria of hyperglycemia and glycosuria. The presence of varicose veins was recorded only if the patient had either extensive varicosities, varicose ulcers, a history of thrombophlebitis, or of surgical treatment of varicose veins. Slight, clinically insignificant, superficial varicosities were not included. Diagnosis of disease of the gall bladder was based on roentgenographic evidence of cholelithiasis, a history of colic with acholia and jaundice, or a record of a surgical procedure upon the gall bladder. Gastro-intestinal symptoms alone, no matter how suggestive, were considered inadequate evidence. The presence of discomfort, pain, or swelling in the joints of the lower extremities was noted. Asymptomatic roentgenographic changes in the joints were not recorded, unless actual complaints were offered by the patient. A few cases of generalized arthritis have been excluded from both the obese and

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control series. The diagnosis of vascular disease was based upon any of the following: (*a*) Persistent hypertension of 150/100 or higher, (*b*) unequivocal cardiac enlargement by teleoroentgenogram, (*c*) congestive failure beyond a history of exertional dyspnea, (*d*) retinal hemorrhage, exudation, scar formation, or pronounced sclerosis of the vessels, (*e*) albuminuria greater than 1+, (*f*) formed elements in the urinary sediment in abnormal numbers, (*g*) marked electrocardiographic changes.

Results. Figure 1 represents the age distribution of obese and non-obese subjects and the incidence of certain disorders in these 2 groups.

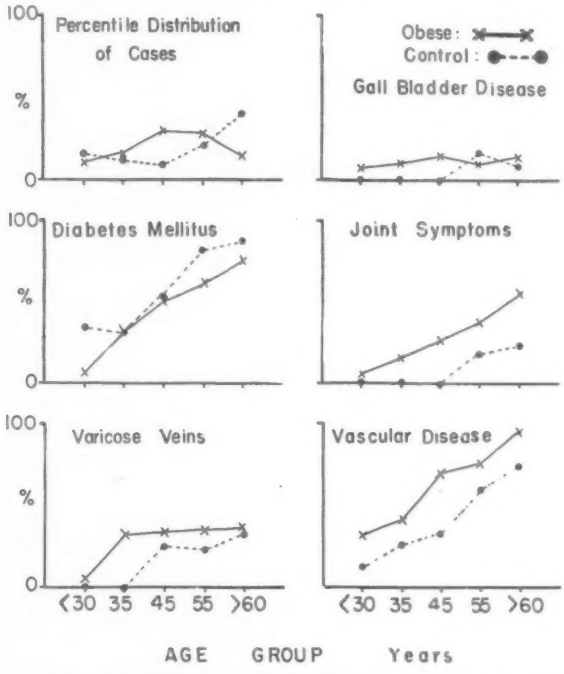

FIG. 1.—Percentile distribution of obese and non-obese subjects according to age and incidence of symptoms and disorders. The groups 35, 45, 55 consist of subjects 30 to 40, 40 to 50, 50 to 60 years of age respectively.

Age. The infrequent occurrence of obesity after the 6th decade suggests a dissociation between obesity and longevity.

Diabetes Mellitus. The high incidence of diabetes mellitus in both groups reflects the specialized composition of the clinic population, and therefore the use of these statistics to study the relationship between diabetes mellitus and obesity is not valid. The basic difficulty lies in the fact that all patients with diabetes attend this dispensary, while only certain overweight patients are referred to this clinic for treatment. It is to be noted, however, that the presence of diabetic patients in approximately equal proportions in the overweight and normal weight groups obviates the possibility that differences between the 2 groups can be ascribed to the diabetic state.

Varicose Veins. These occur about as frequently in both groups beyond the 4th decade, but they appear a decade earlier in the obese

group. Since only clinically troublesome varicosities were included, this represents an important complication of obesity. The changes with obesity which result in varicose veins are not known. In this group, varicose veins occur more often in the male patients than in the female, so that pregnancy cannot be the basic factor responsible for the higher incidence in the obese subjects.

Gall Bladder Disease. The total number of cases of gall bladder disease is not high in either group. This may be in part an expression of the exacting criteria for this diagnosis. Nonetheless, just as with varicose veins, there is an appreciably higher incidence of gall bladder disease among the younger obese subjects. This difference disappears after the 5th decade.

Joint Symptoms. The overweight patients in all age groups are especially apt to complain of pain in the joints of the lower extremities. It is not possible to state, of course, whether obesity produces changes in articular and periarticular tissues as a result of increased pressure, or whether the extra weight serves merely to make minor changes clinically significant. The latter appears to be more probable, since objective findings in the joints are but rarely encountered.

Vascular Disease. Unquestionably diseases of the cardiovascular system are found much more often in overweight patients of all age groups. Hypertensive and arteriosclerotic diseases predominate. Diabetes mellitus occurs a little more often in the control group (61 in contrast to 50%), and hence cannot be correlated with the higher incidence of vascular disease in the obese group. Actually, the inclusion of patients with diabetes mellitus masks an even greater difference in the 2 groups, rather than explains the actual results. Furthermore, the control group includes an unusual number of non-obese patients with nephritis, so that the proportion of patients with vascular disease is unduly high. If these were excluded, the 2 lines of the graph would be further separated.

Hence it is apparent upon comparison of overweight and control groups, each of which contains approximately the same proportion of patients with diabetes mellitus, that obesity is correlated with a decreased life expectancy and is associated with a higher incidence of joint symptoms, gall bladder disease, varicose veins, and cardiovascular diseases. All of these disorders tend, in addition, to appear earlier in the overweight group.

Effect of Obesity Upon Blood Pressure. This study afforded an opportunity to test the general belief that obesity predisposes to the development of hypertension, and that hypertension can be affected favorably by weight reduction. Figure 2 represents graphically changes in the weight and in the systolic blood pressure of 41 obese subjects.

In 12 of 23 patients with hypertension the systolic blood pressure decreased 20 mm. of mercury or more as the weight fell. In 9 others the hypertension was either unaffected or progressed further. In the remaining 2 patients the pressure increased while the weight remained constant. The diastolic pressure followed the systolic in direction of

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change, but the order of magnitude was usually less. It is possible that the remission in some of these would have occurred spontaneously.

It is interesting that only a moderate reduction in weight, 10 to 40 pounds, occurred in all but 1 of the patients whose pressure fell. Although it is recognized that the use of a sphygmomanometer too narrow in relation to the arm circumference results in false high values, most of the patients lost too little weight to alter arm diameter significantly. Indirect evidence of the unimportance of arm size in relation to change in blood pressure is obtained from an analysis of the patients with normal pressure who gained weight. Twelve patients increased in weight by 15 to 93 pounds and not one developed a blood pressure beyond 150/100. Only 2 of the 14 patients initially without hypertension reached hypertensive levels as they gained weight. In

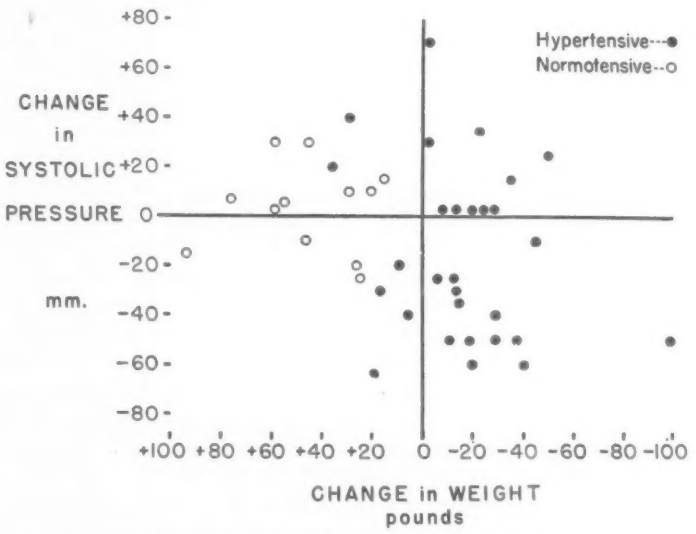

FIG. 2.—Effect of change of weight on the systolic blood pressure.

4 others, who already had hypertension, the pressure fell toward normal despite an increase in body weight. It is apparent that the levels of blood pressure and of weight are not closely correlated. Although hypertension was present more frequently in the obese patients, a gain of weight was rarely productive of hypertension, and a loss was correlated with a drop in pressure in about one-half of the cases. The latter finding is particularly significant in view of the usual progressive course of hypertension.

It is not possible to state that, if these patients had never become obese, the development of vascular disease could have been avoided. The higher mortality in the overweight group suggests that obesity exerts an unfavorable influence upon vascular disease once it has appeared. This study indicates that one manifestation of vascular disease, hypertension, can be minimized in some patients by reduction

of weight. It should be remembered, however, that the level of pressure is of less importance than the state of the vascular system as a whole. Hence a decrease in blood pressure, when obtained, cannot be interpreted as evidence that the unfavorable mortality associated with obesity has been canceled.

Therapy. Adequate records were available of the attempts at weight reduction in 67 of the 87 patients who weighed 200 pounds or more. In diabetic patients the diet was restricted in calories with definite stipulation of the proportions of carbohydrate, fat, and protein. In the others the daily intake included at least 70 gm. of protein. The calories varied from 1000 to 2000, with 1200 the most frequent prescription. This was distributed among 3 or more feedings. The patient was instructed by an experienced dietitian and then seen at intervals of 2 or more weeks. Seven patients received thyroid medication without acceleration of the weight loss.

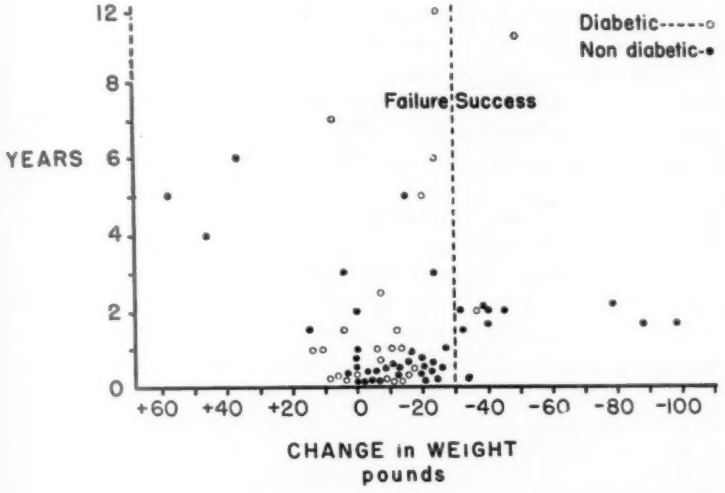

FIG. 3.—Results of attempts to reduce permanently the weight of 67 obese subjects weighing 200 to 484 pounds.

The results of treatment are presented in Figure 3. Of the 67 patients, 19 failed to reduce their weight or actually gained, and 12 others lost less than 10 pounds. The weight of 24 patients decreased 10 to 30 pounds during intervals of several months to 12 years. Only 12 subjects lost 30 pounds or more. Of these, 11 had not relapsed at the end of 2 years or longer. No information was available concerning the subsequent course of the 12th patient. If reductions of 30 pounds or more without subsequent relapse are considered significant in patients who weighed 200 to 484 pounds, therapy was successful in only 1 of every 5 obese subjects. Temporary reductions of weight are not included in the group treated successfully. It is possible that some of the patients who were reduced successfully after 2 years of observation will relapse ultimately. These might well be replaced,

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however, by patients in the 10 to 30 pound weight loss group who reduced their weight further. It is rather surprising to find that the greatest reductions were recorded in the non-diabetic group, since more continuous attention to the diet might be expected from the diabetic patient. This may be partially explained by the fact that most of the extremely obese people were not diabetics. Our criteria of success demand a permanent reduction. By this standard the program employed for reduction failed in about 80% of the cases. The reason for this high proportion of failures deserves consideration.

Discussion of Results of Therapy. Since the laws of thermodynamics unquestionably apply in obesity,[9,12] weight control necessitates adjustment of the caloric intake and expenditure. All obesity results from eating more food than is needed by the body. Social habits, hereditary elements, nervous and endocrine factors may all be present, but they are effective only insofar as they stimulate excessive appetite or reduce caloric expenditure. It has been demonstrated repeatedly that a negative caloric balance will eventually result in a loss of weight,[8] although at times this may be masked temporarily by retention of water.[7] Why then has therapy been successful in only a few patients?

Most writers, in describing successful treatment of obesity, present largely results of short-term studies.[3,4,5,6,8] Only one other attempt at long-term statistical evaluation of results has been found.[11] In this group three-fourths of the patients eventually regained most of the weight lost initially. Short-term studies neglect the fact that weight reduction must be permanent, if the complications of obesity are to be avoided or minimized. In accordance with the criteria for success adopted in this study, a relapse canceled a previous loss in weight. It is possible, furthermore, that our results would have been better with a less obese group. Certainly a loss of 10 to 30 pounds, considered a failure in our patients with marked obesity, would be proportionally much more significant in subjects weighing less than 200 pounds.

Failure must be ascribed to an inability to change permanently the dietary habits of the patient. This does not appear to be a consequence of hypothalamic lesions of the type which have been produced experimentally in rats, monkeys and dogs, with resultant obesity if free access to food is allowed.[1,2] Careful scrutiny of records and patients has revealed only 11 cases of disorders of the nervous system of all categories in a total of 141 patients. This infrequent finding can hardly be proposed as an explanation for a persistent habit of overfeeding, even if it were assumed that all these lesions involved the diencephalon. Neither can responsibility for failure to reduce weight be relegated to disorders of the endocrine system. The patients with thyroid dysfunction who attend this clinic fall into the control rather than the overweight group. Out of a total of 25 patients with myxedema now under observation in this clinic, only 1 is obese.

The rôle of economic factors in failure to adhere to the diet is difficult to evaluate. Patients who attend the dispensary are often unable to provide for themselves a separate reducing diet. Many of them are housewives constantly exposed to the temptation of food.

It is possible that under more favorable circumstances some of these patients could reduce their weight. On the other hand, similar difficulties are frequently encountered in our experience with office patients in better economic circumstances. Apparently some individuals, irrespective of economic status, prefer the pleasures of overeating to the advantages of a normal nutrition.

It might be thought that the problem of obesity is one of diminishing importance under present conditions of food rationing. This does not, however, appear to be true. The excess calories are obtained from an increased consumption of carbohydrate foods. It must also be remembered that many of the meats now available contain a high proportion of fat.

Since moderate restriction of calories fails to produce permanent weight reduction in so many cases, alternative modes of therapy and types of diet deserve consideration. Increased exercise and thyroid medication can be dismissed briefly, for our experience with their futility coincides with that of others.[4,8] Sporadic exercise usually stimulates the appetite out of proportion to the small increase in total caloric output. Desiccated thyroid in moderate amounts has little effect on the metabolism of euthyroid individuals, since the hormone is inactivated.[14] With larger doses, undesirable symptoms of hyperthyroidism appear, and the effect of the increased appetite cancels the higher caloric output.

Both lower and higher caloric diets have been used in the treatment of obesity. Marked limitation of intake to a diet yielding only 400 or 500 calories daily has been advocated.[3,5] This régime naturally results in more rapid loss of weight than do the 1200 or 1400 calorie diets. If sufficient protein is included, a negative nitrogen balance can be avoided.[13] This program, however, can be followed for only comparatively brief periods.[11] Evans, a leading exponent of this régime, presents only the amount of weight lost acutely. In a recent report he notes that 121 patients lost on the average 21.7 pounds in 8 weeks.[5] Comparable results were obtained with our régime during the initial acute period. The high percentage of failure in our cases and the apparent success of other clinics can be explained by differing criteria. We have defined success in terms of permanent weight reduction rather than in terms of ability to lose weight acutely. It has already been pointed out that if the complications of obesity are to be avoided, the weight reduction must be permanent. Relapses are common following periodic drastic caloric limitation, just as they are with the more moderate régime. The reports of Newburgh[8] and of Evans[3,5] present no data permitting statistical evaluation of the permanency of their results. In selected patients, however, such a régime may produce satisfactory weight control.

A less marked restriction of calories to about 2000 daily offers a rational alternative plan of therapy, since caloric expenditure of most patients is higher. Under this plan an ordinary diet is prescribed, altered sufficiently to produce a small negative caloric balance. Weight decrease is then slow and continues over a long period of time. Reduction is accomplished through the inculcation of correct eating habits

rather than through a régime which cannot be long continued. It does seem to be true that in those who reduce successfully by this gradual method, subsequent control is facilitated.

In this clinic no correlation has been found between the number of calories in the assigned diet and the permanency of the weight reduction. Immediate success was common with almost any régime containing 2000 calories or less, if the diet was followed. This is represented graphically by the large number of patients who lost up to 30 pounds during periods of several months (Fig. 3). Ultimate success was much more rare. It must be recognized that a diet which is metabolically sound fails in a great many cases to produce any lasting correction of the obesity. Too much attention to immediate success obscures these poor ultimate results. Less emphasis ought to be placed upon calories and more upon the dietary habits of the patient, so that over a sustained period the intake will remain less than the expenditure of energy. The procedure by which a particular patient is to be persuaded to alter his habits of eating must necessarily be individualized.

Summary and Conclusions. 1. The complications associated with obesity have been studied in 141 obese subjects and compared with those in 100 control subjects.

2. An unusually high incidence of varicose veins, of joint symptoms confined to the knees and ankles, and of hypertensive cardiovascular disease was found in the obese group, particularly in subjects less than 40 years of age.

3. In obese patients with hypertension, the blood pressure fell in approximately one-half of the patients as the body weight was reduced. Hypertension usually did not appear in obese individuals as their weight increased further.

4. The experience of a large metabolic out-patient department with attempts at weight reduction has been reviewed. Success, based upon a permanent weight loss of 30 pounds or more, was obtained in only a minority of the cases.

5. Reëducation in basic eating habits is essential for permanent reduction. The actual daily negative balance of calories is of much less importance.

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NUTRITIONAL IMPROVEMENT OF CHILD MENTALITY*

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Mental energy is a product of 2 factors—capacity and intensity; the one is determined by heritage and maintained by essential nutrients, especially proteins, lipids, water and anions, while the other factor depends on immediate availability of dextrose, oxygen, vitamins and cations. Metabolic disorders affecting the capacity factor or brain structure tend to produce irreversible anatomic lesions, while nutritional disorders affecting cerebral function tend to produce reversible biochemical lesions. The rôle of some essential nutrients has been evaluated in the mental activity of experimental animals but the applicability of this knowledge to children is a moot question. Since multiple nutritional deficiency predominates, the pertinent problem is to determine the effect of malnutrition on retarding mental function.

Despite the difficulty of evaluating the nutritional status of children at various ages and the task of excluding underlying diseases affecting mental growth, we have, nevertheless, been able to study the effects of nutritional improvement on child mentality in 182 children from 2 to 9 years of age, half institutionalized at the Fifth Avenue Hospital and New York City Children's Hospital and half out-patients at the Heckscher Institute and at the Senior Author's office.

Table 1.—Effect of Nutrition on Mentality

	Malnourished Groups			
	41 retarded		50 normal	
	Range	Average	Range	Average
Age	2–8 yrs.	3 yrs. 10 mos.	2–10 yrs.	4 yrs. 8 mos.
I.Q.	20–90	45	95–145	110
Interval	1–7 yrs.	3½ yrs.	1–3½ yrs.	2 yrs.
I.Q. change	−8 to +44	+10	−12 to +55	+18
	Well-nourished Groups			
Age	2–8 yrs.	4 yrs. 10 mos.	2–10 yrs.	5 yrs.
I.Q.	20–90	52	95–140	110
Interval	1–8 yrs.	3½ yrs.	1–3 yrs.	2 yrs.
I.Q. change	−20 to +11	−0.3	−25 to +20	−0.9

Group 1 included 41 mentally retarded and 50 normal children malnourished at the time of the first mental test and well nourished at the time of the second test. Group 2 included 41 retarded and 50 normal children, well nourished at the time of the first test and still well nourished at the time of the second test. Each group was equated for chronologic age, I.Q., and interval between Kuhlmann-Binet or

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Stanford-Binet tests. The data in the tables below reveal an average rise of 10 points for retarded and 18 points for normal children of Group 1 in contrast with an average of zero change for the retarded, and a −0.9 change for the normal in Group 2. The greater variability shown by higher standard deviation of I.Q. in Group 1 in comparison with Group 2 is probably due to the initial variations in nutrient deficiency and individual responses to nutritional therapy. The significance of this difference in I.Q. change in favor of the malnourished group is 2.43, indicating that chances are 99.2 in 100 that the difference is greater than zero.

TABLE 2.—I.Q. CHANGES IN MENTALLY DEFICIENT CHILDREN

	Range	Average	Standard deviation
Malnourished Group			
Age	2 yrs. 1 mo. to 7 yrs. 10 mos.	3 yrs. 10 mos.	1 yr. 5 mos.
I.Q.	22 to 82	45	16
Interval	8 mos. to 7 yrs.	3 yrs. 7 mos.	1 yr. 6 mos.
I.Q. change	−8 to +44	+10	12
Well-nourished Group			
Age	2 yrs. 7 mos. to 7 yrs. 7 mos.	4 yrs. 10 mos.	1 yr. 5 mos.
I.Q.	22 to 88	52	19
Interval	8 mos. to 8 yrs. 9 mos.	3 yrs. 4 mos.	2 yrs. 1 mo.
I.Q. change	−20 to +11	−0.3	6

Intercorrelations by the Pearson Product-Moments method:

	Malnourished	Well-nourished
Age initial *vs.* I.Q. rise	$-.56r \pm .08P.E._r$	$-.003r \pm .106P.E._r$
I.Q. initial *vs.* I.Q. rise	$-.199r \pm .10P.E._r$	$-.025r \pm .106P.E._r$
Interval *vs.* age	$-.098r \pm .10P.E._r$	$-.210r \pm .102P.E._r$
Interval *vs.* I.Q. rise	$-.221r \pm .102P.E._r$	$-.034r \pm .106P.E._r$
Age *vs.* I.Q.	$+.23r \pm .102P.E._r$	$-.007r \pm .106P.E._r$

There is a significant correlation between the age at the time of the first test and I.Q. rise. A correlation of −.56 is a clear indication that the younger the malnourished child when nutritional therapy is instituted, the greater the chance of improvement in mental function. Indeed, the sharp decline in average I.Q. rise for the malnourished group after the age of 4 years suggests that irreparable damage is to be expected in older children. Flexibility of I.Q. change during the first 4 years of life bespeaks of reversibility in mental development, while relative constancy in I.Q. change in older children bespeaks of irreversibility in mental development following prolonged malnutrition. The slightly positive correlation between the length of interval and I.Q. rise in the malnourished group as compared with the zero correlation of the well nourished group suggests that as long as 2 years may be necessary to bring about the average gain in I.Q. following nutritional therapy.

Summary. 1. The effect of nutritional improvement on child mentality has been determined in 182 children, 2 to 9 years of age, half institutionalized and half out-patients, for a period of 14 years.

2. The group of children malnourished at the time of the first mental test and well nourished at the time of the second test showed a rise of 10 points for the retarded and a rise of 18 points for the mentally normal, in contrast with an average zero change for the group well nourished at the time of the first test and still well nourished at the time of the second test.

TABLE 3.—I.Q. CHANGE/AGE IN MENTALLY DEFICIENT GROUP

Age	Malnourished		Well-nourished		Difference
	No. of cases	Average I.Q. change	No. of cases	Average I.Q. change	
2	11	+13.0	5	+2.4	+10.6
3	15	+14.4	7	−2.8	+17.2
4	8	+ 5.3	10	−1.8	+ 7.1
5	0	..	8	+1.6	
6	5	+ 1.6	9	−0.7	+ 2.3
7	2	+ 0.5	2	+1.0	− 0.5

TABLE 4.—I.Q. CHANGE/INTERVAL IN MENTALLY DEFICIENT GROUP

Interval	No. of cases	Average I.Q. change	Range
6 mos. to 11 mos	11	+ 5.6	− 4 to +20
12 mos. to 18 mos.	12	+ 6.8	0 to +26
19 mos. to 25 mos.	7	+10.7	− 2 to +28
26 mos. to 32 mos.	6	+11.3	0 to +23
33 mos. to 5 yrs.	5	+ 0.6	−10 to + 9

3. The younger the malnourished child when nutritional therapy is instituted, the greater the chance of improvement in mental function since the I.Q. rise is insignificant after 4 years of age.

SALMONELLA INFECTION IN MAN

A REPORT OF 5 CASES WITH AUTOPSIES IN 2 CASES, AND A REVIEW OF THE CLINICAL ASPECTS

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IN little more than half a century which has elapsed since Salmon and Smith, in 1885, first isolated the organism which they believed to be the cause of hog cholera, there has come an ever-growing awareness of the importance of salmonella infection in man. We now know that hog cholera is due to a filterable virus, and that the suipestifer organism of Salmon, a natural inhabitant of the intestinal tract of hogs, is but a secondary invader responsible for the septicemic manifestations. Nevertheless, isolation and identification of this and other organisms related to the typhoid, paratyphoid group, now all included under the generic name of Salmonella, have assumed increasing significance in a group of infections of varying severity frequently encountered in

clinical practice. Our knowledge has been placed on a firmer footing since the introduction of a schema of classification by White[23] and Kauffmann[17] based on antigenic analyses, by means of which more than 100 types of salmonella have been identified to date. They are at present classified into 6 groups (A, B, C, D, E, F), depending on their biochemical and serologic reactions, the latter being based on agglutination tests with sera against the somatic and flagellar antigens of the organisms. Since a multiplicity of sera is required, and since some of these organisms at times show variations in antigenicity, the final identification of a strain often becomes a difficult matter, beyond the resources of the average hospital laboratory. For this reason, several Salmonella Centers have been organized where all the necessary serologic work can be performed.

Not all salmonellas have been associated with the disease in man, though it is likely that they are all potentially capable of producing such disease.[4] Furthermore, the severity of the clinical manifestations varies with the infecting organism. For instance, of the five common salmonellas, *S. paratyphi A* and *B*, *S. typhi murium*, *S. enteriditis*, and *S. choleræ suis*, infection with *S. typhi murium* is the form most frequently encountered in the United States, and in 90% of the cases it results in a mild gastro-enteritis.[7,20] On the other hand, by far the largest per cent of septic infections is due to *S. choleræ suis* (suipestifer). It thus becomes a matter of practical importance to identify the infecting organism as soon as possible, not solely for the epidemiologic implications, but also as an aid in prognosis and treatment. For example, if the causative organism is the *S. enteriditis* of Gärtner or the *Typhi murium* of Breslau, and the patient has recovered from the acute enteritis, we need no longer be concerned about him, provided the stool cultures have become negative; but with some of the other organisms the course may be more serious. Thus, *S. parathypi A* produces a typhoidal course with fever and bacteremia but usually no enteritis; the *Schottmueller paratyphi B* causes enteritis, fever, sometimes visceral abscesses, and later may produce healthy carriers; while the *S. suipestifer* may occur in epidemic form when it is usually mild, or in the sporadic form when it is often severe and complicated by abscesses in various organs. During the past 2 years the following 5 cases have been observed on the medical and surgical services of the Israel Zion Hospital which exemplify the protean nature of the disease.

Case Reports. Case 1. J. R. (116481), a 52 year old white male, was admitted to the hospital on 10/23/43, as a private patient, because of fever, weakness of the left arm and leg, and stupor of 24 hours' duration. About 2 weeks prior to the present illness he developed a sudden pain in the left side of the abdomen and fever which subsided in 2 days. On the day before admission, while at work, the patient experienced a severe chill. He was given some whiskey and sent home. A physician was called who found a temperature of 101° F., paralysis of the left arm, and some voluntary resistance to neck flexion. The following morning these signs had increased and, in addition, there was weakness of the left leg. The patient was hospitalized with an admission diagnosis of encephalitis.

The temperature was 104° F., the pulse 110, and the respirations 30. The blood pressure was 170/70. The hemoglobin was 98% (Sahli), the red cell count 4,890,000, and the white cell count 15,600 (63% stab neutrophils, 16% segmented neutrophils, 16% lymphocytes, 9% monocytes). A spinal tap yielded 5 cc. of bloody fluid under 8 mm. of mercury pressure. The blood chemistry showed 170 mg. of glucose per 100 cc., 30 mg. urea per 100 cc., an icteric index of 38, and a direct positive van den Bergh.

A neurologic consultant found the patient comatose, with moderate neck rigidity but no Kernig's sign, paralysis of the left upper and lower extremities, and a bilateral positive Babinski sign. In view of the bloody tap he felt the case was one of subarachnoid hemorrhage, although he could not rule out an inflammatory process. A second spinal tap was performed which showed clear fluid with 68 mg.% of glucose, and 5 to 6 white blood cells per c. mm. A culture of the spinal fluid was negative.

On 11/1/43, a blood culture was reported positive for bacilli of the salmonella group; these were later identified as *S. choleræ suis*. Two subsequent blood cultures were sterile. A culture of the stool was negative for salmonella, and a urine culture was not done.

Nine days after admission the patient was transferred to the medical service. At this time he presented a septic facies; he was semicomatose, irrational, and delirious. The temperature spiked to 104° F., neck rigidity was quite marked, icterus was evident, and spasticity and tenderness were present in the right upper quadrant.

The patient continued to run a septic temperature, but by 11/13/43 his sensorium had cleared somewhat, and he was more coöperative. A dry, hacking cough now became evident, and there were signs of consolidation at the right base with dulness and subcrepitant râles. On 11/17/43, a pleuritic friction rub was heard in the right axilla, and fist percussion tenderness was elicited over the liver. From here on the course continued steadily downhill, and on 11/21/43 he developed pulmonary edema and died.

The entire duration of his illness was 1 month. Treatment consisted of sulfadiazine, parenteral fluids, and supportive measures.

The final diagnoses included *S. suipestifer* septicemia, *S. suipestifer* brain abscess, cholangitis, and pneumonia.

Autopsy. The postmortem (4 hours after death), was limited to the chest and abdomen. The pertinent findings were as follows:

The right *lung* weighed 690 gm. It was adherent throughout its entire surface to the chest wall and diaphragm. The pleura was covered with a shreddy, yellowish-green, partly organized fibrinopurulent exudate extending on to the diaphragmatic surface of the lung. The consistency of the upper lobe was markedly increased. On section, the upper and part of the middle lobe showed many granite-red, granular appearing patches of consolidation. There were a few cavities, up to the size of a cherry, which were filled with frank pus. The walls of these cavities were not clearly defined and consisted of shreddy-appearing lung tissue. The lower lobe showed no evidence of consolidation but appeared poorly ærated and of bluish color. The left lung weighed 420 gm., was moderately congested on section, but appeared normal otherwise. The pleural surface of the right dome of the diaphragm was covered with a thick and largely organized fibrinopurulent exudate which was in apparent contiguity with the exudate of the diaphragmatic surface of the right lung. Corresponding to this area, an accumulation of frank, greenish-gray pus was found below the *diaphragm* on the right dome of the liver. The subphrenic abscess extended into the *liver* parenchyma proper and, on section, a fairly large part of the upper right liver lobe was involved. The liver tissue in this area was partly transformed into a necrotic débris. The rest of the liver parenchyma showed the central veins to be fairly well discernible as dark, reddish specks, and the periphery of the lobules showed a distinct yellowish tinge. The *gall bladder* was somewhat enlarged and moderately tense, and contained clear-green, viscid bile. The spleen was enlarged (weight 220 gm.), and of soft consistency. The capsule was dull. On section, a plum-

sized abscess cavity containing frank pus was found near the hilum. The Malpighian follicles and trabeculæ were ill defined. The small and large intestine showed scattered areas of thinned mucosa and vascular congestion, but were otherwise normal.

On *microscopic examination*, the pleural surface of the lung was covered with a thick layer of partly organized fibrin throughout which were many neutrophils and round cells scattered and in focal collections. There were numerous pigment-laden macrophages. The lung parenchyma showed many areas in which the alveoli were filled with masses of partly organizing fibrin with scant cellular elements. There was an occasional large focal collection of neutrophils. Throughout were scattered macrophages containing brown pigment. In the *spleen* was a large infarct. Included in this area, and at the periphery, were seen several arteries the lumina of which were occluded by granulation tissue consisting of capillaries, fibroblasts, lymphocytes, and histiocytes. A few circumscribed abscesses were seen. The liver contained large cavities, the borders of which consisted of a layer of neutrophils with varying numbers of histiocytes, fibroblasts, and lymphocytes. The centers of the cavities contained fibrin and neutrophilic exudate. Beyond this area, many of the liver cords were replaced by fibroblasts, lymphocytes, and varying amounts of connective tissue.

Pathologic Diagnoses: S. suipestifer septicopyemia; confluent bronchopneumonia with abscess formation, right lung; subphrenic abscess; abscess of the liver; abscess of the spleen; acute tracheobronchitis; vascular congestion of the intestines; and atherosclerosis of the aorta, moderate. The cerebral symptoms were probably due to metastatic abscess formation in the brain.

Case 2. T. W. (111923), a 60 year old white female, was admitted to the surgical service on 12/26/42, because of pain in the right upper quadrant and right shoulder of 28 hours' duration. This had been followed by a chill and a rise in temperature to 103° F. She had vomited once. One year before admission the patient had an attack of biliary colic; since then she suffered from epigastric distress after meals.

The temperature on admission was 103° F., the pulse 120, and the respirations 24. Physical examination revealed a cyanotic flush about the cheeks, an icteric tinge to the conjunctivæ, and slight tenderness in the right upper quadrant, but no rigidity or rebound. The hemoglobin was 98% (Sahli), the red cell count 5,200,000, and the white cell count 7600 (67% neutrophils, 24% lymphocytes, 9% monocytes.) The urine contained a trace of albumin and a few leukocytes. A blood amylase determination was within normal limits.

Six days after admission the symptoms abated, and the patient was transferred to the medical service with a diagnosis of subsiding cholecystitis and possible edema of the pancreas. From a stool sent to the laboratory for routine tests and culture, a *S. newport* was recovered. A few days later a diagnostic duodenal drainage was instituted and culture of the bile revealed a *S. newport* organism.

The patient was treated with succinyl sulfathiazole until the stool cultures were reported negative. She was discharged 27 days after admission with a diagnosis of cholecystitis due to *S. newport*.

Case 3. E. Z., a 32 year old white male, was admitted to the hospital on 3/7/43. Two days before admission he developed chills, headache, pains in the back and limbs, and fever. The following day there was a recurrence of the chills and fever associated with abdominal cramps and several loose bowel movements. On the day of admission, the patient had a 3rd chill and the temperature rose to 104° F., but by the next day it had dropped to normal.

Physical examination was entirely negative. The hemoglobin was 98% (Sahli), the red cell count 5,000,000, and the white cell count 11,200 (75% neutrophils, 2% eosinophils, 20% lymphocytes, 3% monocytes). A stool culture taken on 3/8/43 was reported positive for *S. typhi murium*. The blood culture was negative. The patient was treated with sulfaguanidine until the

stool culture was reported negative. He was discharged 9 days after admission with a diagnosis of *S. typhi murium* gastro-enteritis.

This patient had a short enteric infection due to *S. typhi murium* with fever, prostration, negative blood culture, but a positive stool culture. This organism, also known as *B. ærtrycke*, is a member of salmonella Group B. It is a natural pathogen of rodents, is pathogenic for man and other animals, and is the most frequent cause of outbreaks of salmonella food poisoning. Without the stool examination, the specific diagnosis would have been missed in this case, as it usually is in many similar cases of diarrhea.

CASE 4. M. O'H. (113126), a 53 year old white female, entered the hospital on 3/13/43, because of diarrhea of 5 days' duration. She had pneumonia when 10 years old. At 28 years of age she had an appendectomy, at 31 years a cholecystostomy, and at 34 years a cholecystectomy. Her present illness began with abdominal cramps and diarrhea following a meal of meat balls and macaroni. At the onset the bowel movements were loose and brownish with no pus or blood; the following day, however, they became foul-smelling, green, and admixed with bright red blood.

The temperature on admission was 99.6° F., the pulse 100, and the respirations 20. The blood pressure was 130/90. The patient appeared toxic and dehydrated. The pertinent physical findings were limited to the abdomen which was extremely obese. There was a large right rectus scar in the lower portion of which was an incisional hernia. There were no areas of tenderness, and no palpable masses. The liver and spleen could not be felt. Proctoscopy revealed an edematous, reddened mucosa, but no ulcerations. Pea soup stools were observed, and contents were obtained for culture.

The hemoglobin was 120% (Sahli), the red cell count 5,950,000, and the white cell count 6500 (57% stab neutrophils, 23% segmented neutrophils, 13% lymphocytes, 7% monocytes). The sedimentation rate was 53 (Westergren). A blood chemistry showed 190 mg. of glucose per 100 cc., and 58 mg. urea per 100 cc. The increased red cell count, hemoglobin, and urea were taken to be an indication of severe hemoconcentration induced by the persistent diarrhea. The stool was positive for blood, mucus, and bile, and on culture revealed a *S. newport*. A blood culture and agglutination tests, however, were negative.

The patient was placed on succinyl sulfathiazole, 1 gm. every 4 hours. The temperature varied between 99° and 100° F., and the cramps and diarrhea persisted. Ten days after admission she suddenly lapsed into a coma. The respirations were shallow, lips cyanotic, and the heart sounds unobtainable. She expired the following morning in spite of stimulation.

AUTOPSY. The postmortem (4 hours after death), was limited to the chest and abdomen. The pertinent findings were as follows:

No free fluid was present in the peritoneal cavity. The stomach and transverse colon were distended. The hepatic flexure of the colon was drawn upward to the gall bladder bed by dense adhesions. The gall bladder was not present. The spleen weighed 180 gm., its consistency was mushy, and the pulp diffluent. Malpighian follicles and trabeculæ could not be distinguished. The liver weighed 1550 gm. and was flabby and friable. The capsule was smooth and glistening. The color was reddish-brown with a distinct yellowish tinge. On section, the parenchyma showed the usual architecture to be partly obliterated by a homogenous, yellowish appearance. The esophagus was normal. The stomach contained a moderate amount of brownish, semi-liquid material. The mucosal folds were somewhat atrophic, and there were streaky hemorrhages along the greater curvature and in the antrum. The small intestine was normal, except the terminal ileum, beginning at a distance of about 20 cm. from the ileocecal valve. Here the mucosa was markedly injected, dark red in spots, and showed a number of pin-point hemorrhages. There were also a number of minute ulcerations of the mucosa. The cecum displayed ulcerations behind Bauhin's valve. The rest of the mucosa of the cecum and large bowel were grossly regular. The pancreas, in general, showed the lobulated architecture to be fairly well outlined, but there was a considerable amount of

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fatty and fibrous interstitial infiltration. There were also seen a number of pin-point, yellowish-white, elevated specks which had the gross appearance of fat necrosis. There was no free fluid in the thoracic cavity. The heart contained a few cc. of yellowish fluid in the pericardial sac. On serial section there were numerous pin-point sized hemorrhages through the walls of both ventricles, which in places gave the myocardium a reddish-brown color. The ostia of both coronary arteries were patent. On dissection, both coronary arteries were patent throughout, though a number of pin-point sized, elevated lipoid specks were seen. The ascending aorta showed many yellowish-white, plum-to-quarter-sized elevated and partly calcified plaques. The left lung weighed 480 gm. The upper lobe was well aerated, the lower lobe congested. There was considerable anthracotic mottling. On section, a large amount of frothy fluid could be scraped off the cut lung surfaces. The color of the lung parenchyma was dark red, and there were a few grayish red, somewhat granular elevated areas grossly suggestive of consolidation. The right lung weighed 550 gm. and was similar in appearance to the left.

On microscopic examination, the heart muscle fibers showed fragmentation. Lipochrome granules were seen at the nuclear poles. In a few patchy areas, the muscle fibers were separated by cellular elements consisting of neutrophils, ymphocytes, plasma cells, and fibroclasts. These cellular elements were situated in a fibrillar network, especially around the larger vessels, but in a lesser degree could be followed into the interstitial spaces. In the lungs, many of the alveoli contained a pale staining, fluid-like material. In some areas, peribronchial collections of lymphocytes were seen. The tubular epithelium of the kidneys was swollen and desquamated in places, obliterating the lumen. There were focal collections of lymphocytes between the tubules. The mucosa of the ileum was ulcerated. However, there was only sparse lymphocytic infiltration of the wall. In the pancreas, an increase in peri- and interlobular fat and connective tissue elements were present. Between the lobules and within the meshes of the fat cells a rich cellular exudate in a fibrinous network was seen. The exudate consisted of many lymphocytes, neutrophils, and plasma cells. There was considerable fibrous replacement of the glandular elements, with fibrosis and patchy hyalinization of some of the Langerhans' islands.

Pathologic Diagnoses: Ulcerative terminal ileitis and cecitis; acute splenitis; petechial hemorrhages of the heart and liver; atherosclerosis of the aorta, moderate; and fat necrosis and fibrosis of the pancreas, moderate. The clinical picture pointed to brain involvement, although no examination of the brain was permitted.

Case 5. E. H., a 24 year old white male, was admitted to the hospital on 4/19/43 because of abdominal cramps and diarrhea of 6 days' duration following a meal of sausage, fresh ham, and sauerkraut. The onset was associated with chill and a temperature of 102° F. The frequent bowel movements were not controlled by the usual symptomatic therapy. The cramps were colicky in character and generalized at first, but during the next 2 days they gradually localized in the left lower quadrant.

The admission temperature was 101.8° F., the pulse 70, and the respirations 20. The eyes and pharynx were congested. The heart and lungs were negative. Examination of the abdomen revealed spasm and tenderness in the left lower quadrant, and peritoneal rebound. There were similar findings in the right lower quadrant, though of lesser degree.

The urine was negative. The hemoglobin was 104% (Sahli), the red cell count 5,320,000, and the white cell count 12,000 (50% stab neutrophils, 24% segmented neutrophils, 17% lymphocytes, 9% monocytes).

Because of the duration of the complaints with diarrhea and pharyngeal congestion, a typhoid-like illness was suspected, in spite of the localizing signs in the left lower quadrant. Agglutination tests were negative for typhoid and paratyphoid. A stool specimen was positive for blood, pus, and on culture yielded a *S. paratyphi B*. The Widal was not repeated, but 2 subsequent stool cultures were positive for the Schottmueller organism.

The patient was given sulfaguanidine, 1 gm. every 4 hours, and the tem-

perature gradually returned to normal in about 4 days, the diarrhea subsided, and he became asymptomatic. He was discharged from the hospital 20 days after admission following 2 negative stool cultures.

Discussion. *Clinical Manifestations.* Several recent analytical and statistical reviews have helped clarify the various aspects of Salmonella infection.[4,15,20] In general, 3 clinical types may be recognized. Of these the most common is the *gastro-enteric.* It is characterized by a short incubation period (6 to 24 hours), followed by a sudden onset of gastro-enteritis, with fever, abdominal pain, vomiting, headache, and diarrhea. It may vary in severity from the mildest form of enteritis to a cholera-like syndrome terminating in death. There may be signs of localization simulating appendicitis or cholecystitis, the so-called "pseudo-surgical" syndrome.[13] Slocum[21] has commented on the differential diagnosis of staphylococcus and salmonella food poisoning. In the former the incubation period is shorter (2 to 4 hours), and while the symptoms are similar to those of salmonella gastro-enteritis, fever is uncommon and recovery is rapid (6 to 8 hours). The diagnosis of salmonella gastro-enteritis depends on culturing and identifying the etiologic organism, usually from the stool, but only occasionally from the urine or blood. All serologic groups of Salmonella may produce this form of infection, though *S. typhi murium* is the most frequent offender.

The second type has been designated by Bornstein[4] as *Salmonella Fever.* Its course resembles an atypical typhoid with fever, malaise, leukopenia, and usually a slow pulse, though roseola and an enlarged spleen are often absent. The fever may be continuous or spiking with a duration of 1 to 3 weeks. As in typhoid, tracheobronchitis may occur. Localized foci do not occur in this form. The most frequent etiologic organisms in this type of infection are *S. paratyphi A* and *B.*[6,20] However, other salmonellas may be responsible, as was true in Case 4 of our series. The diagnosis depends on isolating the organism from the blood in the earlier stages of the disease, and later in the course by specific agglutination reactions. Stool cultures are seldom positive.

The third clinical type may be called the *septicopyemic.* Its manifestations are protean, and the mortality rate is high. This form is characterized by marked invasiveness, spreading either by contiguity from an infection in the alimentary tract, or through the blood stream. There is a tendency to localize in lungs, bones, and joints; and visceral abscesses are frequent sequelæ. Salmonellas have been implicated in many localized infections including pleural and pericardial effusion,[12] pulmonary lesions,[11] osteomyelitis and pyarthrosis,[9,15] endocarditis,[14] meningitis,[2] and pelvic exudates.[16] When localization occurs, leukocytosis is the rule. The symptoms consist of evidences of sepsis with other findings, depending on the points of localization. Intestinal lesions are usually absent and the causative organism is rarely recovered from the stool. The diagnosis depends on isolating the organism from the blood and/or from infected foci, and on specific agglutination reactions which are usually positive in the later stages of the disease. Members of Group C, *S. choleræ suis* in particular, are most often responsible for this type of infection.

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While in general every case conforms to 1 of the 3 types,[4] it has been pointed out by Seligmann *et al.*[20] that an absolute differentiation is not entirely feasible, since one may merge with another. Nevertheless, such classification is of considerable aid in furthering our understanding of the varied manifestations which may be encountered.

Epidemiology. Salmonella infection may occur in epidemic or sporadic form. While it has been possible frequently to trace the source of an epidemic, the origin of the sporadic case is more difficult to identify. The more common modes of transmission are meats of infected animals, sausage, cream puffs, ice cream, puddings, milk, and polluted water. Contaminated foods are not altered in appearance, taste, or odor, and the presence of such contamination may only be determined by bacteriologic examination. The symptom-free carrier represents a source of potential danger both to himself and to others. In a routine examination of food handlers, there were found carriers of *S. paratyphi B, derby, montevideo, bareilly, give, chester,* and *newport.*[20] The most prevalent organisms were those in Group B, while those in Group C were next. Infection may be carried from person to person by insect vectors or contaminated foods and dishes.[5] The house fly has been implicated as a vector of *S. enteriditis.*[19] Rats and mice are frequently infected with salmonella organisms, and those that recover may act as carriers, their droppings infecting cream fillings in bakeries and other stored foods to which they gain access. A contrary view has been expressed by Bartram *et al.*,[3] who examined the feces of 800 domestic rats and found that these animals are not normally carriers of salmonella organisms. They feel that their importance as vectors has been overemphasized. Several European epidemics,[22] and at least one epidemic in the United States,[10] have been traced to infected ducks' eggs.

Pathologic Anatomy. Specific lesions have not been demonstrated. Intestinal lesions may vary from ulceration to catarrh, and sometimes, at autopsy, the intestinal findings are normal. Recently, Angrist[1] has described the pathologic findings in a case of *S. typhi murium* infection in which the gross and microscopic pictures bore a striking resemblance to typhoid fever. Otherwise, the findings are similar to other bacteremias or septicemias with splenic enlargement, petechial hemorrhages, liver necrosis, and visceral abscesses. Often the infecting organism can be cultured from these lesions.

Diagnosis. In the epidemic form no difficulty should be encountered. The sporadic case necessitates a constant awareness of the possibility of a Salmonella infection being present. All acute diarrheas should have a bacteriologic examination of the stool, while every case of prolonged fever of undetermined origin should have a culture of the blood, urine, and feces. In addition, when specific agglutination tests are being done, those for salmonellas should be included.

Prognosis. As in many bacterial infections, this depends largely on the condition of the patient, and the type, virulence, and dose of the infecting organism. Fatalities are common in infants and debilitated adults, or in those suffering from chronic illness. There were 5 deaths in 51 cases of salmonella fever, and 18 deaths among 49

cases of the septic type collected by Bornstein.[6] Members of Group C, especially *S. choleræ suis*, account for most of the deaths, because of their invasive tendencies. Seligmann *et al.*[20] have analyzed 1000 cases of salmonella infection of all types. Positive blood cultures were found in almost 60% of those due to *S. choleræ suis*, while *S. paratyphi B* was next with 22%. Both of our cases that came to autopsy were due to members of Group C; Case 1 being due to *S. choleræ suis*, while in Case 4 a *S. newport* was the infecting organism. The gastro-enteric form is usually mild, most cases recovering in 3 to 5 days. An occasional fatality occurs.

Treatment. For the present, this must remain largely symptomatic. Abscesses may be drained, and foci removed surgically. Serum therapy has been attempted, and at least 1 cure with rabbit Group C antiserum has been reported.[18] Vaccines may be used both prophylactically and in chronic infections. Sulfaguanidine has been found to be bacteriostatic *in vitro* for *S. choleræ suis* and *S. paratyphi A*, but is without effect on other salmonellas.[8]

Summary and Conclusions. 1. Salmonella infections are more common than is generally recognized.

2. They may be mild and localized, or severe and invasive.

3. Most cases recover promptly; some are fatal in a few days; while others remain ill for a much longer time in a typhoidal state, with or without the development of metastatic abscesses.

4. The diagnosis depends on recovering the organism from the blood, urine, or feces; later in the course specific agglutination reactions may be positive.

5. The symptom-free carrier represents a source of potential danger to himself and the community.

6. Five cases have been presented, illustrating some of the varied manifestations of salmonella infection in man.

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LESIONS IN RATS FED SULFAGUANIDINE IN PURIFIED DIETS

THE EFFECTS OF LIVER OR "FOLIC ACID" CONCENTRATE-BIOTIN THERAPIES

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Profound disturbances, similar in many respects to those observed in vitamin deficiency syndromes, are produced by the administration of sulfaguanidine or sulfasuxidine to growing rats receiving a highly purified diet.[4–7,9–11,17,21,23,24,25,28,31,33,34,36] Many of these toxic manifestations can be prevented or cured by various dietary factors.[4–7,9–11,17,–21,23,24,25,28,31,33,34,36] Hyperplasia of the thyroid gland produced by these drugs has been cured by the administration of thyroid powder or thyroxin.[3,22] However, the effect of dietary factors upon certain other lesions has not been reported.

There is evidence to indicate that some toxic effects are caused by the ability of the sulfonamides to inhibit synthesis of essential factors by the intestinal bacteria. It is recognized, however, that these drugs may also exert a general, systemic effect by interfering with certain vital enzyme systems within the tissues.

The present report is concerned with the lesions observed during the course of sulfaguanidine administration and their evolution or involution under therapy. A more detailed report of the nutritional aspects of this subject will be given in a subsequent paper.

Methods. Weanling, albino rats from the Sprague-Dawley colony were employed. The basal ration had the following composition: sucrose 76, Labco casein 18, salts[18] 4, corn oil 2 and 1 mg. of 2-methyl-1,4-naphthoquinone. In addition, all animals received B vitamins daily in supplement dishes in the following doses: thiamine 30 γ, pyridoxine 30 γ, riboflavin 30 γ, calcium pantothenate 100 γ, and choline chloride 10 mg. Two drops of haliver oil containing 1.3 mg. of d,1-α-tocopherol acetate were given weekly to each rat.

One series of 60 rats was given the basal ration to which 1% of sulfaguanidine had been added, while another series of 48 rats received 0.5% of the drug in the basal diet. This is roughly equivalent to a human dosage of 150 and 75 gm. daily. A group of 25 rats received the basal diet alone. Five animals of the latter group were given, in addition, whole liver substance (Wilson's), comprising 10% of the ration, at the expense of the sucrose. A final group of 5 rats received 1% of sulfaguanidine with 10% of whole liver in the basal diet from the onset of the experiment.

The substances tested for their therapeutic value in the leukopenia which results from the sulfaguanidine administration have been described in a previous publication.[4] With the exception of whole liver and a "folic acid"

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concentrate, the test substances were ineffective. For the purposes of this report the animals are divided into three groups:

A. Seventy rats given sulfaguanidine and ineffective or no treatment.

B. Forty-three rats given sulfaguanidine and liver or "folic acid" concentrate (prepared from liver) plus biotin. The 5 animals which received liver and sulfaguanidine in the basal diet from the onset of the experiment are included here.

C. Twenty-five rats (control) on basal diet.

Rats of Series A and B were maintained on the experiment for 9 weeks before therapy was instituted. Periodic blood studies were made before and after the institution of therapy. At this time laparotomies were performed under ether anesthesia on 21 rats from the 0.5% sulfaguanidine series for the purpose of observing the gross appearance of the liver. Tissue for biopsy was removed from the liver of 6 rats, and they, with 2 others, were immediately given "folic acid" concentrate and biotin.

Seventeen survivors of 4 months of 1% sulfaguanidine administration, all but 2 of which had received liver or "folic acid" concentrate plus biotin, were given thyroxin in doses of 1 γ per gm. of body weight subcutaneously for periods varying from 2 to 6 weeks.

All survivors were sacrificed at the end of the experiment, after more than 5 months of observation. Autopsies were performed on all animals and sections were taken from the heart, lungs, liver, spleen, kidneys, sternum, adrenals, thyroid gland and skeletal muscle.

Results. General Observations. Animals fed sulfaguanidine showed retardation and finally cessation of growth, a debilitated general appearance, and a severe leukopenia. These adverse effects of sulfaguanidine administration are similar to those previously reported. The development of a state of shock in many of the untreated rats was of particular interest. This was characterized by lowered body temperature, general apathy, and flaccidity of the tissues. In these rats great difficulty was experienced in obtaining sufficient blood from the tail veins for a white cell count. What blood could be obtained tended to clot almost immediately. The above symptoms could be prevented or cured in a large majority of the animals by the administration of liver or of a combination of "folic acid" concentrate and biotin.

Mortality Rate. Within 3 months 87% of the rats of group A, but only 13% of the rats of group B died. All of the control animals (group C) survived.

Gross Autopsy Findings. More than one-half of the animals of group A showed *liver* lesions. These consisted of pin-head size and larger, opaque, white spots, beneath the capsule and irregularly scattered over the cut surface. Many livers, particularly those on the smaller drug dosage, showed larger areas of necrosis which involved from 10 to 50% or more of the liver substance. Indeed, in several animals no normal liver tissue could be seen. These livers were greatly enlarged, almost pure white in color, devoid of normal markings, and exceedingly friable. They gave the appearance of massive infarction. Only 2 of the rats of group B showed liver lesions. These consisted of pin-head sized, chalky-white foci. The distribution of the gross liver lesions is given in Table 1.

The *spleens* also showed focal necroses grossly (Table 2). The necrotic foci were 2 to 4 mm. in diameter, a deeper yellow than those

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TABLE 1.—THE EFFECT OF THERAPY ON THE DISTRIBUTION OF GROSS AND MICROSCOPIC LIVER LESIONS PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount of sulfaguanidine in diet	Gross lesions			Microscopic lesions: No lesion			Microscopic lesions: Active* lesions			Microscopic lesions: Healing lesions		
	A	B	C	A	B	C	A	B	C	A	B	C
1.0%	19/32 60%	2/31 6%	0/10 0%	3/31 10%	23/31 74%	10/10 100%	26/31 84%	5/31 16%	0/10 0%	3/31 10%	4/31 13%	0/10 0%
0.5%	18/38 47%	0/8 0%	0/15 0%	7/36 19%	7/8 88%	15/15 100%	27/36 75%	1/8 13%	0/15 0%	13/36 36%	1/8 13%	0/15 0%
Total	37/70 53%	2/39 5%	0/25 0%	10/67 15%	30/39 77%	25/25 100%	53/67 79%	6/39 15%	0/25 0%	16/67 24%	5/39 13%	0/25 0%

* Degenerative or necrotizing lesions with little or no reaction.
A—Rats given ineffective or no treatment.
B—Rats given liver or "folic acid" concentrate plus biotin.
C—Control rats on basal diet without sulfaguanidine.
The numerator of the fractions indicates the number of rats in which the finding was noted.
The denominator of the fractions indicates the total number of rats in the group.

TABLE 2.—THE DISTRIBUTION OF LESIONS IN SPLEEN, LUNG AND HEART PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount of sulfaguanidine in diet	Spleen: Gross lesions, Necrosis or infarction			Spleen: Microscopic lesions, Necrosis or infarction with or without bacterial invasion			Spleen: Microscopic lesions, Healing lesions			Lung: Microscopic lesions, Bacterial emboli, pneumonia, or alveolar cell mobilization			Heart: Microscopic lesions, Focal necrosis or cellular infiltration		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1.0%	11/32 34%	1/31 3%	0/10 0%	17/26 65%	2/28 7%	0/10 0%	7/26 27%	2/28 7%	0/10 0%	21/31 68%	17/30 57%	2/9 22%	1/31 3%	5/31 16%	0/10 0%
0.5%	3/38 8%	0/8 0%	0/15 0%	7/32 22%	0/8 0%	0/12 0%	0/32 0%	0/8 0%	0/12 0%	19/36 53%	2/8 25%	2/12 17%	2/35 6%	0/8 0%	0/12 0%
Total	15/70 21%	1/39 3%	0/25 0%	24/58 41%	2/36 6%	0/22 0%	7/58 12%	2/36 6%	0/22 0%	40/67 60%	19/38 50%	4/21 19%	3/66 5%	5/39 13%	0/22 2%

Letters and fractions as in Table 1.

in the liver and elevated above the surface. They were irregularly distributed. Occasionally more than one-half or even the entire spleen was necrotic. This was suggestive of infarction.

Urinary tract lesions were encountered in the 1% sulfaguanidine series only (Table 3). All of these lesions were caused by urinary obstruction due to stones. The *kidneys* were usually enlarged, pale, soft and edematous. The pelves were greatly dilated. The *ureters* were also frequently dilated, and impaction of stones at the ureteral orifices of the bladder were not uncommon. Stones were also found in the renal pelves, occasionally in the bladder, and even in the urethra. The stones varied in size from sandlike granules to irregular, yellow to brown, hard masses up to 3 mm. in diameter. Several of these were washed free of adherent soluble material and then analyzed qualitatively for sulfonamides. They were found to contain large amounts of free and acetylated sulfonamide with the latter predominating. In a few instances the kidneys were dark brown in color and the surfaces were granular and irregularly pitted. This scarring was interpreted as resulting from a pyelonephritis.

Many of the *lungs* showed pin-head sized, subpleural, chalk-colored foci which were not elevated above the surface. They were seen occasionally in control animals, but were encountered much more frequently in the experimental rats.

Enlargement of the *thyroid* gland to more than twice the normal size was noted in many animals. This finding was as frequent in the treated as in the untreated rats, but was more common in the 1% group than in the group on 0.5% drug.

In some rats the *intestines* were distended with fluid and gas and suggested the picture of paralytic ileus.

No other significant findings were noted grossly. It is worth emphasizing that none of the control rats showed any spontaneous lesions, so that those described may safely be ascribed to the results of treatment received.

Microscopic Findings. Because of the complicated and varied character of the microscopic changes, they will be described first and their distribution noted subsequently.

Liver. The microscopic alterations in the liver include cloudy swelling, hydropic degeneration, various types of necroses, fatty degeneration, hepatitis, bacterial invasion, and varying degrees of repair.

Albuminous degeneration: This may be slight in degree, but in most instances it is severe. However, even when severe, it is commonly the least striking lesion. The swelling of the hepatic cells is at times so great that the sinusoids are all but obliterated. In a number of rats, scattered hepatic cells contain coarse to large, angulated, basophilic cytoplasmic granules. Such cells are conspicuous because of their purple color in the hematoxylin-eosin preparations. The nuclei of the hepatic cells may be normal, but many are enlarged, the chromatin is scanty, and the color is pale. Fragmentation of the liver cords and dissociation of the liver cells is occasionally associated with this, as well as with the more serious alterations in hepatic architecture.

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TABLE 3.—THE DISTRIBUTION OF GROSS AND MICROSCOPIC RENAL LESIONS PRODUCED BY THE PROLONGED ADMINISTRATION OF SULFAGUANIDINE

Amount sulfaguanidine in diet	Gross lesions: Urolithiasis, with hydronephrosis or hydroureters			Gross lesions: Chronic pyelonephritis			Microscopic lesions: Pyelonephritis			Bacterial embolism			Nephrosis			Tubular dilatation			Calcific foci		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1.0%	6/32	5/31	0/10	2/32	2/31	0/10	1/31	5/31	0/10	7/31	0/31	0/10	5/31	2/31	0/10	6/31	15/31	0/10	20/31	25/31	0/10
	19%	16%	0%	6%	6%	0%	3%	16%	0%	23%	0%	0%	16%	6%	0%	19%	48%	0%	65%	81%	0%
0.5%	0/38	0/8	0/15	0/38	0/8	0/15	0/37	0/8	0/15	3/37	0/8	0/15	0/37	0/8	0/15	0/37	0/8	0/15	5/37	0/8	0/15
	0%	0%	0%	0%	0%	0%	0%	0%	0%	8%	0%	0%	0%	0%	0%	0%	0%	0%	14%	0%	0%
Total	6/70	5/39	0/25	2/70	2/39	0/25	1/68	5/39	0/25	10/68	0/39	0/25	5/68	2/39	0/25	6/68	15/39	0/25	25/68	25/39	0/25
	9%	**13%**	**0%**	**3%**	**5%**	**0%**	**2%**	**13%**	**0%**	**15%**	**0%**	**0%**	**7%**	**5%**	**0%**	**9%**	**39%**	**0%**	**37%**	**64%**	**0%**

Letters and fractions as in Table 1.

TABLE 4.—THE EFFECT OF THERAPY ON THE ACTIVITY OF BONE MARROW AND THYROID GLAND IN RATS GIVEN PROLONGED SULFAGUANIDINE TREATMENT

Amount of sulfaguanidine in diet	Bone marrow activity: Hyperplastic			Bone marrow activity: Hypoplastic			Thyroid activity*: Resting			Thyroid activity*: Hyperplastic		
	A	B	C	A	B	C	A	B	C	A	B	C
1.0%	6/28	24/26	....	22/28	2/26	....	12/26	5/25	....	14/26	20/25	
	21%	92%	....	79%	8%	....	46%	20%	....	54%	80%	
0.5%	9/27	8/8	15/15	18/27	0/8	0/15	28/28	5/8	....	0/28	3/8	
	33%	100%	100%	67%	0%	0%	100%	63%	....	0%	38%	
Total	15/55	32/34	....	40/55	2/34	....	40/54	10/33	11/13	14/54	23/33	2/13
	27%	**94%**	....	**73%**	**6%**	....	**74%**	**34%**	**85%**	**26%**	**70%**	**15%**

* Animals which received thyroxin are excluded from the tabulation.

Letters and fractions as in Table 1.

The Kupffer cells are frequently greatly swollen. The sinusoidal lining is often detached, and the space between the liver cells and the sinusoidal lining contains acidophilic granular material. The sinusoidal lumens may contain little or no blood, but considerable granular material.

Hydropic degeneration: The most striking and severe alteration in architecture is produced by an enormous swelling of the hepatic cells. This swelling has frequently progressed to the point of cell-wall rupture. The cytoplasm is colorless and clear except for a few remnants of delicate reticulum radiating from a centrally situated, round nucleus. The nuclei are generally smaller than those of normal hepatic cells and stain more deeply. The cytoplasm does not stain with any of the more common water-soluble dyes. Negative results are also obtained with fat-soluble dyes (frozen sections) including Sudan IV, Nile blue sulfate, and those used in the Lorrain Smith-Dietrich stain. Celloidin sections stained by the Best-carmine technique* show no glycogen in the swollen clear cells. Severe glycogen depletion is apparent throughout the sections. These large cells may be found scattered and single, but more commonly they are grouped in clusters of 6 to 20 cells. They may be found in central, peripheral or midzonal positions. In some animals the hydropic degeneration is extensive, involving many contiguous lobules, and may be so severe that the liver tissue is scarcely recognizable (Fig. 1). Occasionally a few of the degenerated cells contain coarse, angulated, basophilic cytoplasmic granules similar to those seen in cells which have undergone cloudy swelling. Other cells in the same section may show extensive vacuolization with slight to moderate clearing of the cytoplasm. These represent a less severe degree of hydropic degeneration. Generally, however, cells adjacent to the swollen clear cells show a dense, acidophilic cytoplasm.

Necroses: Various types of necroses are encountered. The necrotic foci are also variable in distribution, shape and size. When the necrosis is central, the hepatic cells immediately adjacent to the vein are not involved. The necrotic areas are usually one-third to two-thirds the size of a lobule. Some are elongated and interconnect with one another (Fig. 2). The necrosis is usually coagulative in type, but may be hyaline. With the former, the outlines of hepatic cords and sinusoids may be obliterated, while with the latter, not only are the cords and sinusoids intact, but the cell outlines may also be discernible. The cells which have undergone hyaline necrosis are shrunken; the nuclei are absent; the cytoplasm is dense, deeply acidophilic and homogeneous. The sinusoidal spaces are dilated and empty. With very few exceptions the necrotic regions and their periphery show no cellular infiltration, but adjacent viable liver cells exhibit varying degrees of degeneration. There is usually a severe proliferation and swelling of Kupffer cells, many of which are desquamated and degenerated.

* Only a few animals were selected for glycogen studies. Care was taken to allow no more than 1 minute between the death of the animal and fixation of a thin slice of liver in absolute alcohol.

Occasionally a small necrotic focus is found immediately subjacent to the intima of a portal vein (Fig. 3). The overlying endothelial cells are swollen and desquamated, while the lumen contains a recent fibrin thrombus.

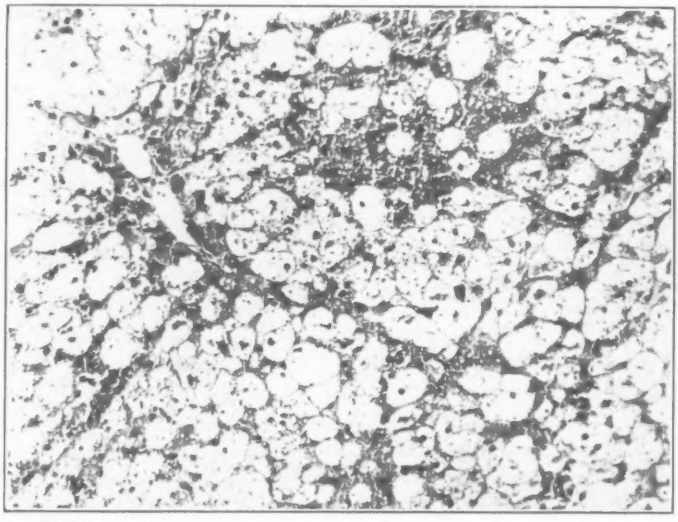

FIG. 1.—Hydropic degeneration of liver. Many large clusters of swollen cells with clear cytoplasm involve several contiguous lobules. Cells adjacent to the clear cells are essentially normal. Rat on 1% sulfaguanidine, untreated.

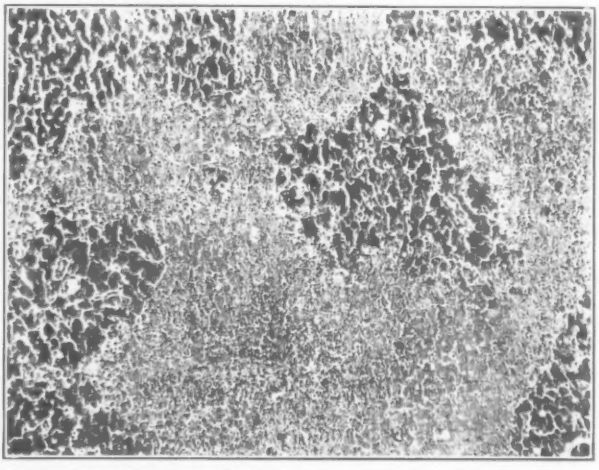

FIG. 2.—Necrosis of liver, coagulative in type. Interconnecting bands of necrosis isolate and surround portions of lobules. There is no cellular reaction to the necrosis. Small focal hemorrhages are present. Rat on 0.5% sulfaguanidine, untreated.

The most extensive necroses are those secondary to infarction and this may involve a part of a lobe or, at times, most of the liver. Slight to severe hemorrhage accompanies the infarctions. The periphery of

the infarcted areas shows no marginal zone of leukocytic infiltration. There is no cellular reaction other than a moderate intensification of the proliferation and swelling of the Kupffer cells seen elsewhere. Many sinusoids and hepatic, as well as portal, veins in the infarcted zones are occluded by recent fibrin thrombi.

The least striking of the necroses involve isolated cells or clusters of cells. These represent the end-stage of progressive degenerative processes. The necrotic cells are in various stages of disintegration and they contribute considerably to the cellular débris present in the areas of degeneration.

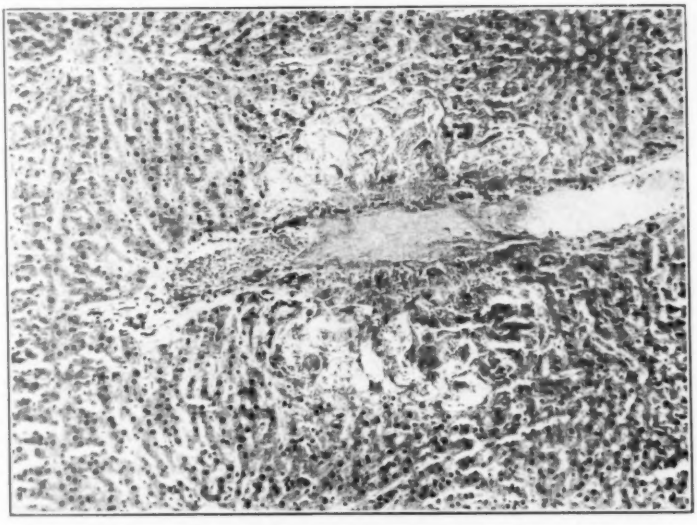

FIG. 3.—Focal necrosis about a vein. A delicate fibrin thrombus occludes the vein in the region of necrosis which also involves the wall of the vein. There is no cellular reaction to the necrosis. Rat on 1% sulfaguanidine, untreated.

Fatty degeneration: Frozen sections stained with Sudan IV, Nile blue sulfate, and by the Lorrain Smith-Dietrich method exhibit droplets of neutral fat and other lipoids in the liver cells near regions of necrosis and hydropic degeneration. The amount of neutral fat and other lipoids in the cells is variable and often great. The distribution of the involved cells is irregular. In some regions the central zones show large amounts of neutral fat only; while in other sections there is little or no neutral fat in the central zones, but the mid-zonal or peripheral zones show both neutral fat and other lipoids in small to moderate amounts. Very little lipoid is found in livers which show minimal or no involvement.

Hepatitis: The only general reaction to the various degenerative and necrotizing processes is a proliferation of the Kupffer cells which are swollen, at times to the size of hepatic cells, and frequently desquamated. Some of these cells contain dark, almost black pigment and some contain green pigment. However, no iron is demonstrable by

the Prussian-blue reaction and most of the Kupffer cells contain no pigment, although phagocytized cell débris and vacuoles are seen occasionally within the cytoplasm. In and near the necrotic zones the Kupffer cells are also necrotic and their débris constitutes a large component of the sinusoidal content.

Bacterial invasion: Many, but by no means all, foci of coagulation necrosis contain large, centrally situated masses of bacteria. These are usually gram-positive cocci or bacilli, but in some instances gram-negative bacilli are also present. The tissues adjoining the necrotic area are usually free of bacteria. Occasionally bacterial masses are found within the lumen of veins occluded by recent fibrin thrombi. Neither the foci invaded by bacteria nor the adjoining tissues show

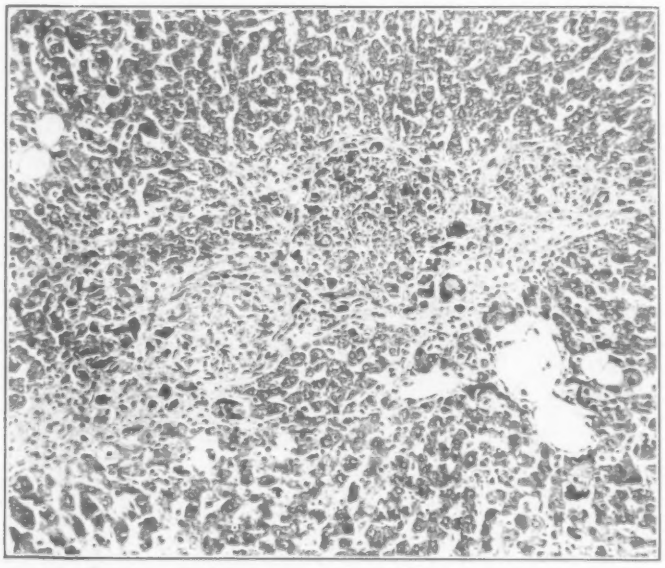

FIG. 4.—Scar in liver. There are numerous proliferated bile ducts and giant cells in the scar tissue, along with pigment-laden phagocytes, endothelial cells, and some remnants of cellular débris. Rat on 0.5% sulfaguanidine, untreated.

any reaction to the presence of the microörganisms. No bacteria are seen in areas of hyaline necrosis or in the vicinity of necroses which involve single cells or small cell groups. Infarcted zones are only occasionally involved by bacteria. Bacteria are found only in animals which died spontaneously.

Repair: Evidence of repair is found in relatively few animals. There are four indications of this process. The most obvious indication is the presence of large scars (Fig. 4). These scars are composed of loosely arranged or fairly dense connective tissue, moderately rich in fibroblasts, and relatively avascular. Large monocytic phagocytes containing yellow pigment or with vacuolated cytoplasm are loosely scattered throughout the connective tissue. Many scars also contain lymphocytes in small foci and also more widely and more sparsely

distributed. Many of the scars also contain proliferated bile ducts and sometimes groups of liver cells. Occasionally a small hepatic lobule is surrounded by scar tissue.

A second indication of repair is the presence of multinucleated giant cells (Fig. 5). These giant cells contain 3 to 8 nuclei. The origin of these cells appears to be mostly from Kupffer cells, but also from bile duct epithelium, and occasionally from liver cells (Fig. 6). The appearance of the nuclei varies accordingly. Those derived from the Kupffer cells are darker and smaller. The cytoplasm is commonly pale, but occasionally it is deeply acidophilic. The giant cells are frequently numerous, but are found in only a few of the animals. Some are seen in relation to scar tissue, but more often they are present in various parts of a hepatic lobule which shows no scarring.

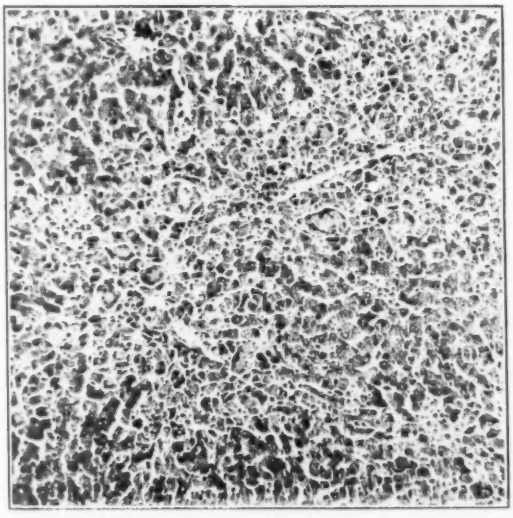

FIG. 5.—Repair of liver lesion, the formation of numerous giant cells. These appear to be formed by endothelial cells. There is much fragmentation of the liver cords and a small amount of cellular débris is present. Rat on 0.5% sulfaguanidine, untreated.

Bile duct proliferation is found in a small number of rats. Although pronounced in scar tissue, this proliferation is also seen in the peripheral zones where no scar tissue is present.

A fourth but less obvious indication of repair is an alteration of architecture without scar tissue production. The lobules are of various sizes, irregular in outline, and their anatomic limits are ill-defined. In these sections there are many isolated hepatic cells which are conspicuous by their deeply acidophilic cytoplasm. Many hepatic cells are binucleated, and multinucleated syncytial liver cell masses are encountered (Fig. 6). The nuclei of other cells may vary considerably in size and chromatin content. Some nuclei are very large, hyperchromatic, and show a very coarse chromatin network. Occasional nuclear monstrosities are noted (Fig. 6).

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No bacteria are found in the regions which show evidence of healing. In 1 animal a chronic purulent perihepatitis is seen.

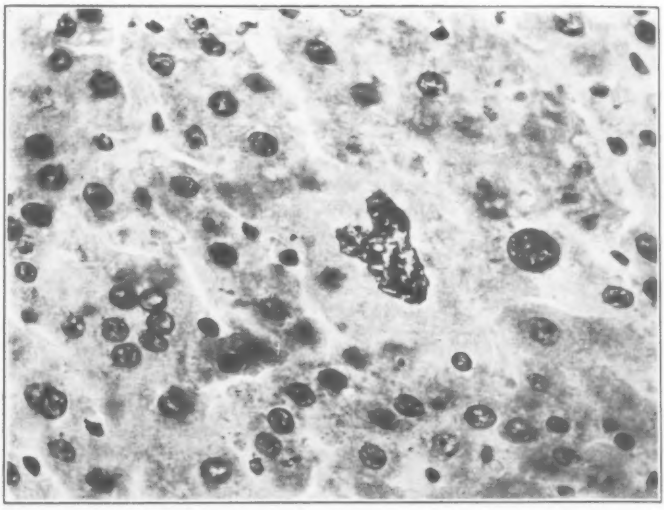

FIG. 6.—Repair of liver lesion, the formation of syncytia by cells of the hepatic cords. Note giant cell with 9 nuclei; the nuclei vary in size and staining-intensity. There is a nuclear monstrosity. Rat on 1% sulfaguanidine treated with liver.

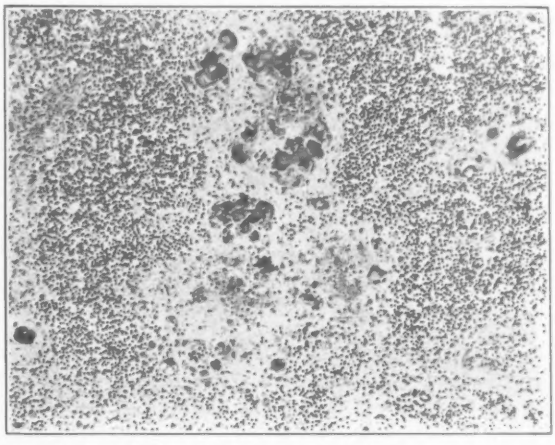

FIG. 7.—Repair of splenic lesions. There are irregular, collagenous foci which contain small masses of deeply basophilic amorphous material (calcific ?). The collagenous foci are infiltrated scantily by endothelial cells, some of which possess foamy cytoplasm. Rat on 1% sulfaguanidine, treated with "folic acid" concentrate plus biotin.

Liver sections of some rats which received liver or "folic acid" concentrate therapy show minute hematopoietic foci and occasional nucleated red blood cells in the sinusoids.

Spleen. Rounded foci of coagulation necrosis, with and without bacterial masses similar to those observed in the livers, are present

in the spleen of many rats. As many as 4 to 6 foci are seen in some sections. They vary in size from one-third to twice the size of a follicle and may involve the periphery of splenic corpuscles or the pulp. Thrombosis of splenic vessels is frequent. This thrombosis is of recent character and no reaction in the vessel wall is seen even when bacteria are present in the lumen. No exudation accompanies the necrosis of splenic tissue.

Many spleens show small or extensive infarctions, sometimes involving as much as three-fourths of the spleen. The infarcted zones show no marginal leukocytic infiltration. Profuse proliferation of endothelial cells is frequent and is associated with a corresponding paucity of lymphocytes and an almost complete absence of splenic corpuscles. The endothelial cells frequently contain a large amount of hemosiderin. Some spleens show a progression of this process with the diffuse laying down of collagen fibers, obliterating the normal sinusoidal architecture. These alterations may involve large portions of a spleen, but in other regions of the same section little to moderate alteration may be present.

There are a number of rats in which the necrotic foci are partially or completely replaced by dense scar tissue. In this scar tissue there are deposits of deeply basophilic amorphous material suggestive of calcium salts; large, lipophage-like cells, monocytes, and occasional multinucleated giant cells are also present (Fig. 7).

In the same animal which shows purulent perihepatitis a similar perisplenitis is noted.

Many animals which received liver or "folic acid" concentrate plus biotin therapy show pronounced leukopoietic activity in the splenic pulp. This is absent in animals not so treated.

Sternal Bone Marrow. The histologic picture of the sternal marrow varies from almost complete aplasia to intense hyperplasia. In the severely hypoplastic marrow cytoplasmic blobs without nuclei are noted, as well as many large, pale, endothelial-like cells. The latter are frequently degenerated and the nuclei pyknotic. Megakaryocytes in these sections are greatly reduced in number and show similar degenerative changes.

Heart. Lesions in the heart are infrequent. They are isolated, minute, and usually situated subepicardially in the left ventricle. Several foci of necrosis involving one or two muscle fibers are encountered. Occasionally neutrophilic leukocytic infiltration of two or three myocardial fibers and the associated stroma is noted. Similarly small foci of fibroblastic proliferation are present in several animals. In a few rats several myocardial capillaries are found occluded by bacterial masses. The adjoining tissues show no reaction to the presence of the bacteria.

Lungs. Subpleural collections of large, almost colorless cells with very small, round, central nuclei are frequent. These cells often completely fill the alveolar spaces and resemble alveolar phagocytes (Fig. 8). Occasionally these cells are also seen about bronchi and vessels.

Many animals exhibit bacterial masses in alveoli and the lumens of large blood-vessels and alveolar capillaries. As a rule, the pulmonary tissue shows no reaction to the presence of the bacteria. In some lungs alveoli adjacent to the bacteria contain edema fluid and occasionally fibrin. In one instance the reaction consists of severe swelling, proliferation and desquamation of alveolar cells. Leukocytes are generally absent. Vessels near the bacterial masses are often occluded by recent fibrin thrombi. The walls of vessels containing bacterial emboli show no reaction. In one control rat an interstitial pneumonitis is present.

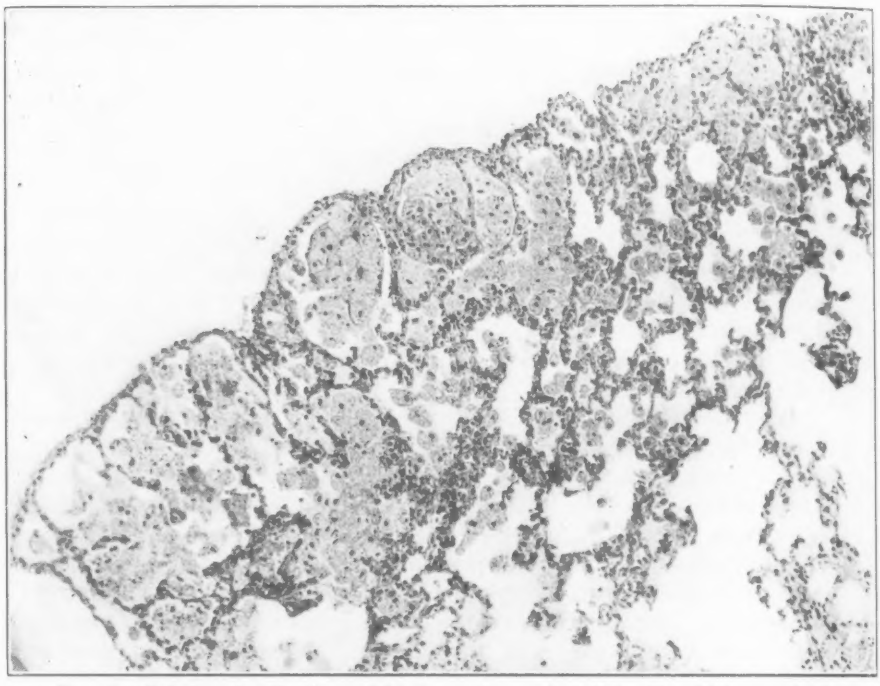

FIG. 8.—Subpleural collections of large, swollen endothelial cells which completely fill some of the alveoli. Rat on 1% sulfaguanidine treated with "folic acid" concentrate plus biotin.

Kidneys. Cloudy swelling of tubular epithelium is present in many animals, but it is severe in only a few, where it is associated with casts and débris in the lumens. Deposits of structureless, deeply basophilic material are frequent in the medulla, but may be seen occasionally in the cortex as well. These deposits, which resemble calcific material, lie between the tubules and do not involve the latter. They appear to fill spaces lined, at least partially, by delicate endothelial-like cells (lymphatic spaces ?). There is no inflammatory reaction adjacent to these deposits. In some rats there are subepithelial deposits and encrustations at the pyramidal tips, and papillary projections bulging with this calcific (?) material may project from the pyramids into the

pelvis. Some of these papillæ have become detached and lie as foreign bodies in the urinary pelvis. All animals with the latter finding were afflicted with gross uroliths.

Some of the rats which exhibit bacteria in the liver or spleen also show bacterial emboli in the kidneys. An occasional glomerulus is partially or completely obliterated by the bacterial masses. Inflammatory reactions are absent in all but one instance. In one rat, proliferation of glomerular epithelium and endothelium is present and early glomerular adhesions are demonstrable.

In a number of rats, varying degrees of pyelonephritis are encountered. Some of these inflammations are focal in distribution, while others involve the entire kidney diffusely.

Indications of past urinary obstruction are seen in moderate to severe dilatation of the collecting tubules, particularly at the tips of the pyramids, and occasionally also of the convoluted tubules. This finding is more frequent with the larger sulfaguanidine dosage. Occasionally a delicate scaffolding of fibrils outlining angular spaces within dilated tubules suggests the site of crystal deposits.

Adrenal Gland. Although this organ was not sectioned in all rats, generally no significant lesion is found. In several instances isolated, minute, cortical, focal necroses and small hemorrhages are noted.

Thyroid Gland. Hyperplasia of the thyroid is frequent. The degree of hyperplasia varies considerably and is often of severe degree. The hyperplastic glands are composed of relatively small acini lined by pale, exceedingly tall epithelium with empty, and in some instances, virtually non-existent lumens.

Skeletal Muscles and Vessels. No lesion of skeletal muscles or of vessels is noted.

Distribution of Microscopic Findings. For the purpose of a better perspective, the degenerative and necrotizing lesions of the liver have been grouped together and tabulated under "active lesions" in Table 1. All lesions of the liver suggestive of repair have likewise been grouped together in this table under the heading of "healing lesions."

The distribution of significant microscopic lesions in the spleen, lungs and heart is given in Table 2. Microscopic renal lesions are classified and tabulated in Table 3.

The sections of bone marrow are graded from 0 to 4+ according to the activity exhibited. On an arbitrary basis, the bone marrow with 3+ or 4+ activity is classified as hyperplastic, while bone marrow with 2+ or less activity is classified as hypoplastic in Table 4.

The sections of thyroid gland are similarly graded in this table according to the degree of hyperplasia, from 0 to 4+. Because the thyroid glands of many control rats show 1+ hyperplasia, this is taken as the upper limit of activity of the resting state. Activity above this grade is classified as "hyperplastic." The thyroid glands of all animals which received thyroxin, with the exception of one, are in a resting state microscopically.

Observations in Laparotomized Animals. Grossly only 2 of the livers observed at operation showed foci of necrosis. The remaining 19

appeared normal or exhibited varying degrees of pallor. Hydropic and other degenerative changes were noted microscopically in 5 liver sections taken from 6 of the 8 animals which subsequently received "folic acid" concentrate plus biotin. Foci of necrosis were present in 2 of the 5.

One animal with a normal liver at laparotomy died within 24 hours after the operation and then had a completely infarcted liver. This liver was enlarged, pale, almost white, soft and friable. The cut surface was almost completely devoid of structural markings. This infarction could not be ascribed to operative vascular damage.

The 2 animals showing foci of liver necrosis at operation and 4 of the others died within 3 days. Five more rats succumbed within 1 month following laparotomy; only 1 untreated rat and all 8 treated with "folic acid" concentrate plus biotin survived to the end of the experiment, approximately 3 months after operation. On microscopic section, liver lesions were observed in 11 of the 13 untreated animals, but in only 1 of the 8 animals receiving "folic acid" concentrate plus biotin. The liver of this treated animal showed healing as well as active lesions.

Relation of Hepatic Lesions and Bone Marrow Activity. A close parallelism exists between the pathologic alterations of the liver and the activity of the bone marrow. In 76% of the animals whose liver shows necrosis or hydropic degeneration, or both, the bone marrow is hypoplastic (0 to 2+). On the other hand, in 77% of rats with normal liver the marrow is hyperplastic (3+ to 4+). Eighty-five % of the rats with hypoplastic marrow (0 to 2+) show the above hepatic lesions, whereas 84% of the rats with maximally active marrow show no hepatic lesion.

Discussion. Clinical[8,13,15,26,27,35] and experimental[1,2,9,12,19,20,29] reports of hepatic lesions produced by sulfonamides indicate that they are largely degenerative and focally necrotic. There is good basis for the belief that any one of the sulfonamides in common clinical use may be capable of producing similar disturbances. Thus, Menten and Andersch[26] have recently described degenerative and necrotizing lesions of the liver in children given various sulfonamides and they have also found disturbance in function.

In the present experiment, similar results were obtained and the sole indication of inflammatory reaction in the liver or spleen, with few exceptions, is the proliferation and swelling of endothelial cells. The absence of exudative reactions was a dominant feature and this may be related to the associated leukopenia.

There are indications that the larger areas of necrosis are infarctions. The association of the necrotic foci with vascular thrombosis supports this assumption. The explanation for the thrombotic vascular occlusions may be sought in the hemoconcentration incident to shock, the attendant increased blood viscosity, the diminished blood flow, and the consequent increased tendency of the blood to clot.

It appears from the present experimental results that the hepatic changes exclusive of infarction are to a large extent reversible and

reparable. The administration of liver or "folic acid" concentrate and biotin to afflicted animals resulted in the repair of necrotic foci and in the return of degenerated hepatic tissue to normal in a considerable proportion of the animals. This is indicated not only by the difference in incidence of liver lesion in the untreated (A), as compared with the treated (B) group, but also by the fact that 5 rats which showed degenerative lesions at laparotomy, exhibited normal livers following treatment with "folic acid" concentrate plus biotin. Such reparative processes may occur spontaneously, but in a much smaller number of animals, provided that thrombotic vascular occlusions have not resulted in irreparable damage inconsistent with life. It is worthy of emphasis that none of the 5 animals which received liver therapy from the beginning of sulfaguanidine administration showed liver lesion.

The similarity of certain aspects of experimental sulfaguanidine-induced hepatic lesions with those encountered clinically with other sulfonamides makes it appear probable that their etiologic background is identical and that such clinically encountered hepatic lesions may be susceptible to liver or "folic acid" concentrate and biotin therapy. Since liver therapy is already being employed to combat leukopenia incident to sulfonamide administration, the above findings may furnish another reasonable basis for employing this corrective therapy. The questions of whether or not the prophylactic administration of liver or of "folic acid" concentrate and biotin will lessen the incidence of other side effects as well, and whether or not such prophylaxis will interfere with the effectiveness of the sulfonamides, await future clinical investigations.

The basic cause of focal necrosis of the liver which occurs in typhoid fever and occasionally also in other severe infections is not known. It is highly probable that there is severe depletion of the tissue vitamins in these conditions. It is possible that the focal necrosis of the liver in typhoid fever may be caused by infection-induced vitamin depletion and that it may be related to that produced experimentally by drug-induced vitamin depletion. If this be correct, then the focal hepatic necroses secondary to infections may also be susceptible to amelioration by the administration of liver or "folic acid" concentrate and biotin.

The bacterial invasion must be considered an agonal or postmortem phenomenon. The absence of tissue reaction to the presence of the bacteria and the absence of bacteria in any of the animals which did not die spontaneously, support this belief.

There are numerous references in the literature demonstrating the protective effects of various dietary constituents upon the toxic manifestations of certain drugs. The present study emphasizes again the need for careful standardization of the diet in drug toxicity studies. It is evident that the relative amounts of various dietary factors may influence strongly the apparent toxicity of a drug.

The close parallelism between the pathologic alterations of the liver and disturbance in bone marrow functions admits of several explanations. It is possible that the liver produces a factor necessary for leukopoiesis. Disturbance in function of the liver cells, which pre-

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cedes or accompanies morphologic alterations of the liver, may depress or inhibit the formation of the leukopoietic hepatic factor(s). Another possibility, which is perhaps more likely, is that chronic sulfaguanidine poisoning produces disturbances in cellular metabolism which are manifested both in the liver and in the bone marrow.

Whatever the explanation, the administration of liver or "folic acid" concentrate and biotin largely corrects the disturbances of cellular metabolism in both the liver and bone marrow as is indicated by the high incidence of normal livers and associated hyperplastic bone marrow in animals so treated.

There is at least one type of cellular metabolic disturbance caused by the sulfonamides which does not appear to be mediated through a vitamin deficiency, and this is hyperplasia of the thyroid gland. Hyperplasia of the thyroid, observed in the present experiment and previously reported by others,[3,22,23] is prevented or cured by the administration of thyroid powder or thyroxin.[3,22] This is also indicated by the present results. Apparently the sulfonamides interfere with the production of thyroxin because these animals have a basal metabolic rate below normal in spite of the hyperplastic state of the epithelium.[3,22]

The collections of large monocytic cells in the lungs may be regarded as an expression of a generalized hyperplasia and mobilization of endothelial cells which reaches its highest development in the liver and spleen. It is true that subpleural foci of endothelial-like cells similar to those found in experimental rats were seen in a number of the control animals. However, the incidence and severity of the lesions were much greater in the animals which received sulfaguanidine than in the controls. The necrotic foci described in human lungs[27] secondary to sulfonamide therapy were not observed in the experiments here reported.

Minute focal myocardial necrosis and focal myocardial cellular infiltration incident to sulfonamide administration have been reported in man and animals.[14,32] In man the cellular myocardial infiltration has been largely eosinophilic.[14] In the present experiments myocardial involvement was minimal and no eosinophils were noted.

With the exception of the basophilic deposits suggestive of calcium salts, the changes in the kidneys are identical to those previously observed with this and other sulfonamides.[1,16] The interstitial position of this material, usually in what appears to be a lymphatic space, is puzzling and requires further investigation. Randall's theory[30] of the genesis of renal calculi receives beautiful experimental confirmation in the presence of masses of the basophilic material beneath the surface epithelium of the renal papilla. Even more striking and confirmatory of this theory are papillary masses of this material covered by epithelium. Some of these papillæ are still attached by a narrow pedicle to the renal papilla, while others lie detached as foreign bodies within the renal pelvis.

Conclusions. 1. Rats maintained on a purified basal diet to which has been added 0.5% or 1% sulfaguanidine show severe symptoms and

pathologic changes which become maximal after 2 months of drug ingestion and terminate fatally in about 90% of the animals.

2. The drugged animals show deceleration and cessation of growth and a debilitated general condition. Terminally shock becomes manifest. The signs of this condition are apathy, diminution in body temperature, flaccidity of skin and muscles, failure of cut veins to bleed, and increased viscosity of the blood with increased tendency to clot.

3. The pathologic changes include progressive hypoplasia of the bone marrow which may attain the state of aplasia; degenerative and necrotizing hepatic lesions; focal necrosis and lymphoid exhaustion of the spleen; hyperplasia and mobilization of endothelial cells in the liver, spleen and lungs; hyperplasia of the thyroid gland; occasional minute foci of myocardial degeneration and necrosis with cellular infiltration; urolithiasis with the complications secondary to urinary obstruction; and nephrosis.

4. The administration of liver or "folic acid" concentrate plus biotin to animals suffering from the sulfaguanidine effects reduced the mortality rate from 90 to 14%. Under the influence of this therapy the liver and splenic lesions tended to disappear or to heal and the bone marrow became hyperplastic. The hyperplastic state of the thyroid remained unaffected except by the administration of thyroxin.

5. The experimentally demonstrated curative action of liver and "folic acid" concentrate plus biotin on the toxic sulfaguanidine effects suggests the clinical trial of these preparations as prophylaxis against certain of the toxic effects of sulfonamides. Widespread clinical use of liver or "folic acid" concentrate in sulfonamide therapy must await clinical investigation of the question whether these substances interfere with the effectiveness of the sulfonamides.

We are indebted to Merck & Co., Inc., for the B vitamins; to the Lederle Laboratories, Inc., for sulfaguanidine; and to the Wilson Laboratories for solubilized liver.

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DRUGS USED IN CLINICAL DIAGNOSIS*

REVIEW OF RECENT LITERATURE

THE application of drugs in diagnosis constitutes a chapter of conspicuous importance in the evaluation of disease. Although isolated instances are encountered earlier, it is for the most part a development of the past 25 years. Drugs are used for securing information concerning the structure and function of organs and systems. They have been employed in the study of disorders of the liver, kidney, heart, circulation, central, peripheral and autonomic nervous systems, gastro-intestinal tract, blood, endocrine systems and nutrition. They provide means of ascertaining the powers of absorption, fixation, secretion, excretion and the metabolic state of tissues and organs. The object of the present paper is to review some of the enterprise in this field, more especially those phases which have received particular attention in the past few years.

Bromsulphalein. The dye, phenoltetrabromphthalein sodium sulphonate, was introduced as a test of liver function in 1925 (Rosenthal and White[102]). The test depends on the fact that the compound is almost entirely excreted by the liver into the bile in normal individuals and that in liver dysfunction there is delay in its removal. The principle of the technique involves determining the amount present in the blood at intervals following its intravenous injection. The technique appears to test the capacity of the reticulo-endothelial system (chiefly the Kupffer cells) to remove this foreign substance from the blood stream rather than the capacity of the liver cells to excrete it in the bile. The two functions can be readily separated in the dog (Mills and Dragstedt[75]), and in man (Cantarow and Wirts;[18] Wirts and Cantarow[131]). The removal from the blood stream takes place rapidly, 85 to 95% in 5 minutes, while the excretion in the bile is a matter of several hours. Furthermore, in early bile stasis due to obstruction of the common duct, the excretion of the dye

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into the bile may be delayed while the other function, namely, its removal from the blood stream, may still proceed at the normal speed.[131]

There seems to be some doubt concerning the relationship between the blood retention of the dye and the histologic changes in the liver. There is one report which states that abnormal retention is always associated with structural change in the liver as shown by sections of the human liver, although normal retention does not exclude such changes (Bauman and Orr[13]). There is another, however, which states that histologic changes in the liver are not always found to account for the abnormal dye retention (Kruger and Gerber[50]).

In the original test, a dose of 2 mg. per Kg. was injected intravenously and a sample of blood was taken in 30 minutes. The normal standard was complete clearance at this time,[102] the presence of more than traces of the dye in the blood being taken as abnormal. Various modifications have been explored with the view of increasing the sensitiveness of the method. The dose of the drug has been increased, and various plans for testing the blood have been suggested involving one or more samples at intervals varying from 5 to 60 minutes. There remains a great deal of uncertainty in the results of these studies especially because in the case of every modification there is need to revise the standard normal values which are often allowed to rest on an insufficient number of cases. There is the suggestion of increasing the dose to 5 mg. and determining the curve of dye concentration by blood samples taken at intervals of 5 minutes (MacDonald[63]). The value of this type of curve is in need of further study. The test appears to be more sensitive than the original when made with two blood samples, one at 5 and the other at 15 minutes, the first never showing more than 60% and the second rarely more than 5% retention in normal people (Deutsch[23]). There is the indication from comparisons in the same patients that the 5 mg. dose is more apt to detect abnormal liver function than the 2 mg. dose. The larger dose was used with a single specimen of blood tested at 30 minutes (Helm and Machella[36]), and the assumption was made that the 5 mg. dose of dye disappears from the blood completely in 30 minutes. It was subsequently shown, however, that with this dose about one-fourth of young normal controls retain some dye after 30 minutes, although all show complete disappearance in 45 minutes (Mateer *et al.*[69]).

There is a fairly large literature on the application of bromsulphalein as a test of liver function in various diseases. It has been extended in the past few years. In the test using 5 mg. and 5, 15 and 30 minute blood samples, liver function has been found abnormal in heart failure (Bernstein *et al.*[15]) although it is to be noted that the test may prove misleading in heart failure because of incomplete mixing of the dye in 15 minutes.[23] Patients with chronic pulmonary tuberculosis frequently show abnormal dye clearance (5 mg. dose, 15 and 30 minute intervals) and the incidence rises abruptly in those with amyloid disease.[50] A high incidence of abnormal liver function has been found in a wide variety of cases of low-grade chronic illness (Stiles *et al.*[116]). These matters are in need of further study because the method used assumed complete clearance of the 5 mg. dose in 25 minutes and others have shown that many normals take longer to clear this dose completely.

Benzoic Acid. The use of sodium benzoate as a means of testing liver function was introduced in 1933 by Quick. It is based on the fact that in man the liver combines glycine with benzoic acid to form hippuric acid which is then excreted in the urine (Quick[90,91]). Various factors involved

in the interpretation of the test have been studied in recent years. In the way in which the test is applied, one determines the amount of hippuric acid recovered in the urine after a dose of benzoic acid. Since the body does not store glycine (Quick[89]), the amount of hippuric acid recovered tests not only the capacity to conjugate benzoic acid with glycine, but the power of glycine synthesis.[89] The capacity to synthesize hippuric acid from benzoic acid is limited by the available glycine.[90] In healthy individuals about 1.5 gm. is the maximum amount of sodium benzoate which the liver can convert into hippuric acid per hour. This peak production is obtained by a dose of 4 gm. of sodium benzoate and cannot be raised by increasing this dose (Probstein and Londe[86]). The simultaneous administration of glycine may greatly increase the hippuric acid excretion (Probstein and Londe;[86] Quick, Ottenstein and Weltchek[93]). In view of these facts reduced excretion of hippuric acid after giving benzoic acid may represent either reduced synthesis of glycine or reduced conjugation of hippuric acid. The two functions may be distinguished (Probstein and Londe;[87] Graña and Vizca[29]). In one study[93] there were 30 patients in whom, after a dose of sodium benzoate, the hippuric acid excretion was less than normal. In most of these the chief difficulty seemed to lie in diminished power to synthesize glycine because the simultaneous administration of glycine raised the hippuric acid recovery. In a smaller number the chief difficulty lay in impaired power to combine glycine with benzoic acid since the simultaneous administration of glycine and benzoic acid did not enhance the recovery of hippuric acid. The use of the hippuric acid test for liver function would be invalid if renal excretion of hippuric acid were slower than the rate of its production. It has been found, however, that the renal excretion of hippuric acid proceeds at a rate about 2.5 times that of its synthesis (Schwei and Quick[106]). Since excretion may be diminished in renal disease, the value of the test for liver function may be enhanced by a determination of the rate of excretion of injected hippuric acid (normals, about 3.5 gm. per hour). There are conflicting opinions concerning the question whether the volume of urine affects the excretion of hippuric acid, one study failing to find any relation,[86] while in another the results indicate a direct relationship (Machella, Helm and Chornock[67]). The rôle of body weight among adults is also undecided, a correlation having been found by one group (Hepler and Gurley[38]) and denied by another.[67] A more recent study of the intravenous test has again affirmed a decided influence of the body size on the amount of hippuric acid recovered after the standard dose in subjects without liver disease (Scurry and Field[107]).

The original hippuric acid test involved the administration of 6 gm. of sodium benzoate orally and the recovery of the hippuric acid excreted in the ensuing 4 hours in the urine by precipitating and weighing the crystals.[90] Analytical modifications have been introduced. The solubility of hippuric acid in urine is reduced to one-fifth when the urine is saturated with sodium chloride (Weichselbaum and Probstein[124]). The addition of ammonium sulfate for that purpose seems to be more satisfactory, the loss from dissolved hippuric acid being fairly constant at about 0.1 gm. per 100 cc. of urine (Marron[68]).

It has been suggested that an oral dose of 4 gm. is more satisfactory because it suffices to tax the capacity of the liver fully and has a lesser tendency to cause vomiting than the 6 gm. dose.[86] A dose of 3 gm. is sufficient for children weighing under 40 kg. (Londe and Probstein[57]). The standard result for normal individuals is the recovery of 3 to 3.5 gm. of benzoic acid as hippuric acid in the urine in 4 hours after an oral dose of

4 or 6 gm. of benzoic acid,[86,89] or the recovery of 2 gm. or more in 2 hours after the 4 gm. dose.[86]

An intravenous test has also been devised[93] (Lipschutz[56]). In the one most commonly used,[93] 1.77 gm. of sodium benzoate (1.5 gm. benzoic acid) are injected intravenously in 20 cc. of water. In normal individuals about 50% (0.7 to 0.95 gm.) is recovered in the urine in the form of hippuric acid in 1 hour by the precipitation method. It has been suggested that an ether extract and formol titration method is less likely to yield falsely high values (Moser, Rosenak and Hasterlik[76]). An intravenous method avoids disturbance of digestion and takes less time to complete.

The intravenous hippuric acid test is abnormal in many diseases (Bartels[10]): hyperthyroidism, primary liver disease and chronic infectious arthritis. The fact that it is normal in severe muscular dystrophy suggests that muscle plays little or no part in the conjugation of glycine with benzoic acid. The oral test shows the liver function impaired in abdominal operations and after ethylene, ether and spinal anesthesias (Boyce[16]). There is impaired liver function not only in primary hepatic disease but in mechanical jaundice and cardiac failure (Lindboom[55]). Psychoses are frequently associated with impaired synthesis of hippuric acid, especially marked in catatonia, these cases showing a rise of synthesis after improvement by treatment (Quastel and Wales[88]). There is some indication that the capacity of the liver to conjugate hippuric acid is related to the severity of hyperthyroidism although the test is not of much value in the management of the disease (Haines, Magath and Power[33]). While there may be some correlation between plasma prothrombin and the hippuric acid excretion, the relationship disappears after treatment with vitamin K, indicating that the two functions are independent (Kark *et al.*[42]). The low hippuric acid values in the test after operation may be due to the diminution in the available carbohydrate (Campbell[17]) since glucose administration tends to restore them to normal. In menstruation there is impaired liver function which may be related to the disturbed water balance during this period (Heilig and Kantiengar[35]). The test also gives low values during pregnancy, especially low in toxemia (Neuweiler;[77,78] Hirsheimer;[39] Palmer[84]).

Patients with 50% reduction in the hippuric acid excretion by this test are poor surgical risks.[89] While there is some difference of opinion concerning the value of the test in differential diagnosis of hepatic disease and jaundice (Rennie[95]), a normal hippuric acid recovery in the presence of jaundice suggests biliary obstruction and a low recovery points to toxic hepatitis.[89] This test is more sensitive than bromsulphalein. It has been suggested that it may be too sensitive for practical purposes and that the normal values for the middle and later decades should be lowered (Paulson and Wyler[85]).

Galactose. The use of galactose for the testing of liver function was introduced in 1906 (Bauer[12]). It is based on the fact that this sugar is metabolized exclusively by the liver and independently of insulin (Shay, Schloss and Bell[108]). It is converted into glycogen with greater difficulty than other sugars (Cori[21]) and hence is better suited as a test of liver function. Animal experiments show that the liver, and not muscle, converts galactose into glycogen (Uexküll[119]). It is believed to be superior to levulose or glucose tolerance tests for hepatic function, because tissues other than the liver play a large part in the metabolism of the latter two. The test is carried out in various ways, embodying the administration of the galactose orally or intravenously, and testing either the blood or th

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urine after an interval for its content of galactose. In the method of oral administration and urine testing the subject with an empty stomach may receive 40 gm. of galactose in a liter of water. The urine may be collected at intervals of 30 minutes for 4 hours. Two normal values may be obtained under these conditions: less than 3 gm. recovered in the urine and the period for this excretion no longer than 2 hours (Krönicke[49]). The 40 gm. dose is slightly above the maximum which the normal man can metabolize[12] (MacLagan[64]). A maximum strain is therefore put on the liver. A modification in the analytic technique limiting the period of fermentation of the urine to 60 minutes increases the accuracy of the galactose recoveries (Lichtman[54]). Others give 40 gm. orally in as little as 250 cc. of water and test the blood for galactose at intervals of 30 minutes for 2 hours[64] or the same dose in 400 cc. and test the blood after intervals of 30 and 60 minutes (Althausen, Lockhart and Soley[4]). In normal individuals, after an oral dose of 40 gm., the range of blood concentration is between 10 and 30 mg. per 100 cc., values above 40 and below 10 being considered abnormal[4] (Meranze, Likoff and Schneeberg[72]). In one study the normal peak values were found to be higher, between 63 and 81 mg. per 100 cc.,[64] the blood samples having been taken at 30 minute intervals for 2 hours.

Because of variable absorption there is some question of the reliability of the oral test and intravenous galactose tests have been devised. In one method (Bassett, Althausen and Coltrin[11]), 1 cc. of 50% galactose solution per kg. is injected intravenously in 5 minutes and the blood is tested 75 minutes later. In this period normal persons clear the blood completely, while patients with hepatitis retain an average of 45 mg. per 100 cc. and those with obstruction 14 mg. per 100 cc.

The galactose tolerance test is used as a means of revealing hepatic dysfunction in various conditions: cirrhosis of the liver, rheumatoid arthritis, surgical operations and pneumonia, and it serves in the differential diagnosis of toxic from obstructive jaundice.[64] Abnormality by this test does not run parallel with the results from other tests such as the bromsulphalein or oral hippuric acid tests.[72]

The test has received special attention in hyperthyroidism (MacLagan *et al.*[65]) and it has been considered of comparable reliability with the metabolic rate in thyroid diagnosis.[4] Impaired liver function may be demonstrated in from 45 to 90% of all cases of hyperthyroidism by the various liver function tests, but the galactose test seems to be more uniformly correlated with clinical signs of severity, namely, basal metabolic rate, weight loss, and duration of the disease (Lichtman[52]). Some have failed to observe correlation of the test with basal metabolic rate.[4] The galactose retention (oral dose and blood testing) has been found abnormally high in 95% of cases of hyperthyroidism and abnormally low in about 90% of cases of myxedema.[4] It is suggested that rapid absorption in hyperthyroidism and slow absorption in myxedema due to altered speed of phosphorylation in the intestinal mucosa may be responsible for the abnormal values,[4] although others believe that while the test is an important adjunct to the diagnosis of hyperthyroidism and that this disease rarely exists with a normal galactose tolerance, neither impaired liver function nor altered gastro-intestinal absorption are sufficient to explain fully the mechanism of the change in disorders of the thyroid.[72] The evidence seems to favor increased rate of intestinal absorption rather than liver damage as the cause of the abnormal galactose tolerance in hyperthyroidism, since in these cases the intravenous test may be normal

when the oral test is grossly abnormal (Barnes and King[9]). Galactose tolerance is abnormal in upper respiratory infections, malignant disease, Bright's disease, and in those who have recently received sulfonamide therapy, but the impairment is most marked in thyrotoxicosis (Rosenkrantz, Bruger and Lockhart[103]). Several of the most recent papers again stress the importance of the galactose tolerance test in hyperthyroidism. It may be used as a diagnostic test (Wilson[130]) in masked thyrotoxicosis, in thyrotoxicosis after iodine treatment, and in cases in which the basal metabolic rate cannot be accurately determined. A normal galactose tolerance helps to exclude hyperthyroidism in patients with elevated metabolism due to other causes; it is more reliable when used in this way because impaired tolerance occurs in a wide variety of disorders. An increased galactose retention as a test for hyperthyroidism is unreliable in the presence of complicating conditions such as have already been mentioned as well as in peptic ulcer, hepatic insufficiency and Paget's disease (Schneeberg, Likoff and Meranze[105]).

Bilirubin. The injection of bilirubin as a means of testing hepatic function was introduced in 1927 (Von Bergmann;[121] Eilbott[25]). The test was developed in this country by Harrop and Barron.[34] Evidence is fairly strong that the injected bilirubin is not stored but excreted by the liver. Numerous studies have been made which indicate the value of this test as a measure of the excretory function of the liver (Soffer[110]). In the conventional method, a dose of bilirubin, 1 or 1.5 mg. per kg., is injected intravenously and the amount remaining in the blood in 4 hours is used as an index of liver function. In many normal people the blood is completely cleared in 4 hours. Some consider excretion impaired if the retention exceeds 5% (Soffer and Paulson[111]), while others accept a retention of 15% or less as normal (Kornberg[48]). A formula has been suggested for calculation which takes into account the fact that the speed of clearance varies with the concentration of bilirubin in the blood, and expresses the result as a "velocity constant of excretion," a method which appears to be especially important for cases with elevated basal concentrations of bilirubin (Weech, Vann and Grillo[123]). This test of liver function seems to be very sensitive. It was found to be more sensitive than the metabolic tests such as that using galactose or benzoic acid and gave approximately the same number of positive results as the bromsulphalein test in one group of diseases of the liver (White, Deutsch and Maddock[126]). Others have found it even more sensitive, and impaired liver function was found by this test to exist months after recovery from catarrhal jaundice at a time when the bromsulphalein excretion test was normal.[48]

Tyrosine. The fact long known that there is increased tyrosine in the urine in liver disease (Lichtman[53]) has been made the basis of a liver function test (Bernhart and Schneider[14]). A dose of 4 gm. of tyrosine in a solution of 250 cc. containing 5 gm. of casein is given orally after an overnight fast and samples of blood are tested for tyrosine 1, 2 and 3 hours later. In normal fasting blood the tyrosyl content is equivalent to from 1 to 1.8 mg. of tyrosine per 100 cc. of blood, and rises during the test to 5.4 mg. after 1 hour, falling off in the subsequent 2 hours. In liver disease, it may rise to high levels, 15 mg. in the first hour, and remain high for several hours. The test, in some cases of hepatic cirrhosis, is more sensitive than bromsulphalein and other common liver function tests. Whether the test relates to a metabolic or excretory function of the liver is not yet established.

Amino Acids. In impairment of the liver function in the dog, there is retention of plasma amino acids after the intravenous injection of casein hydrolysate, and this appears to represent a delay in the function of deamination (Goettsch, Lyttle, Grim and Dunbar[28]). It has also been shown (Lyttle, Goettsch, Greeley, Grim and Dunbar[62]) that in children with portal cirrhosis similar plasma retention of injected amino acids takes place. Such retention does not occur in nephrosis or in severe kidney disease with impaired renal function. The injected amino acids do not reduce the capacity of the kidney for excretion of the end-products of metabolism of the amino acids, since the urea clearance remains normal; also there is no significant effect on amino acid clearance. In normal children the pre-injection amino acid nitrogen in the plasma ranges from 2.92 to 4.63 mg. per 100 cc., and after an intravenous injection of casein hydrolysate in a dose of 12 mg. of amino acid nitrogen per kg., the normal level is restored in 35 to 95 minutes due to diffusion into the tissues and deamination by the liver. In patients with liver disease there is delay in clearing the plasma of amino acids and there is failure of the normal increase in urinary urea and ammonia excretion following the injection. The injection of amino acids, therefore, seems to provide a method for evaluating the deaminizing capacity of the liver. From a previous study (Stewart and Rourke[113]) the conclusion was drawn that in patients with advanced liver disease the non-protein nitrogen level of the plasma returns to the pre-injection value in a manner similar to that of normals after an intravenous injection of a solution of amino acids. These experiments, however, were not so performed as to reveal the delay in the decline of the curve, which appears to be in evidence during the period of the first $1\frac{1}{2}$ hours.

Azorubin-S. This material was first put to use in a test of liver function in 1924 (Tada and Nakashima[117]). It is a dark red water-soluble dye, which is non-toxic in the necessary doses. It is excreted by the liver to the extent of 95%. A dose of 4 cc. of a 1% solution is injected intravenously, and 5 minutes later 40 cc. of a 25% solution of magnesium sulfate is given through a duodenal tube. Samples of duodenal contents are then collected at 1 to 2 minute intervals. In normals the dye appears in 15 to 30 minutes. Its appearance is delayed in diseases of the liver. The value of this test is confirmed in many studies. It is one of the few dye methods which directly tests the excretory function of the liver, since the method requires its recovery from the duodenum rather than its disappearance from the blood as in the case of bilirubin or bromsulphalein. In a group of cases of cirrhosis of the liver, this test was found as reliable as the bromsulphalein and more often positive than the hippuric acid test, and in early chronic hepatitis it was found more often abnormal than either of the other two (Rosenberg and Soskin[101]).

Vitamin K. The utilization of vitamin K in the formation of prothrombin is a function of the liver (Andrus, Lord and Moore;[7] Lord, Andrus and Moore[58]). In the absence of bile in the intestine (biliary obstruction) blood prothrombin falls because of the failure of vitamin K absorption. In hepatic disease blood prothrombin may fall because of diminished capacity of the liver to synthesize prothrombin. In both conditions jaundice may occur. The administration of vitamin K with bile salts causes dramatic improvement in the blood prothrombin in obstructive jaundice (Stewart, Rourke and Allen[114]). Synthetic vitamin K given intramuscularly is similarly effective (Macfie, Bacharach and Chance[66]). This has been confirmed by many (Scanlon *et al.*;[104] Stewart and Rourke;[115]

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Olson and Menzel[80]). On the other hand, hypoprothrombinemia due to liver disease shows little or no response to vitamin K (Allen and Julian;[3] Wilson;[129] Kark and Souter;[43] Smith and Owen;[109] Lucia and Aggeler[61]). There is some response to vitamin K if the liver damage is not severe (Rhoads[97]). The response to vitamin K has been suggested as an aid in differentiation of intra- and extrahepatic jaundice (Lord and Andrus[59]). An intramuscular injection of 2 mg. of menadione was found to raise the plasma thrombin 10% or more in 24 hours in patients with extrahepatic jaundice. Several workers have utilized the response to vitamin K as a means of distinguishing surgical jaundice from severe damage of the liver (Olwin;[81] Abbott and Holden;[1] Allen and Julian[2]). A patient with jaundice who fails to respond to intravenous menadione, 2 mg., repeated in 24 hours, with a considerable increase in the blood prothrombin is not subjected to operation, on the basis that it is in all probability not due to obstruction, but to acute yellow atrophy.[81] The differential response to vitamin K is not absolute and cases of severe jaundice due to parenchymatous liver disease have been encountered which showed good response to vitamin K (White, Deutsch and Maddock[125]). There are many cases of obstructive jaundice in which the extrahepatic disease is complicated by parenchymatous liver disease and in such cases subnormal response to vitamin K occurs (Greene and Bruger[30]). These factors limit the decisiveness of the test in differential diagnosis of jaundice. Various degrees and types of response to vitamin K have been suggested as means of testing the degree of impairment of liver function (Kark, Souter and Deutsch;[45] Kark and Souter[44]). Failure to obtain response to vitamin K may be assumed to represent impaired liver function (Owen;[82] Ziffren, Owen, Warner and Peterson[133]). Additional information may be secured from the vitamin K response.[125] The prothrombin may rise rapidly in obstructive jaundice and in healing acute hepatitis, as distinguished from chronic hepatitis; the damage is widespread and irreversible in acute hepatitis if prothrombin continues to fall in the face of an adequate supply of vitamin K.

Multiple Agents in Test of Liver Function. In the past few years numerous studies have been published in which several drug liver function tests were tried in groups of patients with primary liver diseases as well as other conditions in the endeavor to explore their relative sensitiveness and to define better the special uses and applications of the several tests.[5,6,8,19,22,26,32,37,41,46,47,70,71,73,74,92,94,96,98,100,112,118,120,128] The chief agents represented were benzoic acid, bromsulphalein, galactose, azorubin-S, bilirubin and vitamin K. There have been some comparisons with tests which do not require the administration of an agent such as determination of urinary bilirubin, urinary urobilinogen, cholesterol partition, blood phosphatase, icteric index, Van den Bergh reaction, Hanger's cephalin flocculation test, the Takata-Ara test and others. Opinions which issue from these studies bear on such matters as the effect of age on liver function, the behavior of the liver in various acute and chronic infections, hepatic function in malignant metastasis to the liver, in hyperthyroidism, blood diseases, alcoholism, amyloidosis, heart disease, the use of the tests in preoperative management, as a guide to effectiveness of treatment, and to prognosis, and the differential diagnosis between intra- and extrahepatic jaundice. With respect to many details there is want of agreement arising in part from the differences in technique, limited number of cases in the various groups, and variations in the types of cases studied. Opinions concerning the practical usefulness of liver function tests vary

all the way from those workers who place great reliance on them, to those who find them of little value as a guide either to diagnosis, prognosis or treatment. There is a tendency to ignore the results if they are out of line with the clinical aspects of the case. The sensitiveness of the various tests is ranked differently by different workers. For example, some find the bromsulphalein more sensitive than the hippuric acid test, others find the reverse. Some find the galactose test uniformly successful in differentiating intra- from extrahepatic jaundice; others find it of little value.

It may be well, however, to bring together some of the more important generalizations which seem to be fairly well established by the cumulative experience with these tests in recent years. There seems to be little doubt that with due regard for their limitations, the drug tests for hepatic dysfunction often supply important practical information. The liver has many functions and each of the methods tests a different function. The bromsulphalein test probes the capacity of the reticulo-endothelial system to fix a foreign dye. The bilirubin test probes the capacity of the liver cells to excrete into the bile a normal constituent of the blood; and the azorubin-S test, its capacity to excrete a foreign dye into the bile. The hippuric acid test measures an enzymatic system, the detoxifying power of the liver in the synthesis of glycine and its conjugation with benzoic acid to form hippuric acid. The galactose tolerance tests the glycogenic activity of the liver. Amino acid tests the deaminizing power of the liver. The results of the various tests do not run parallel. In far-advanced liver disease all liver function tests are abnormal, but in lesser degrees of liver damage, impairment is selective and the functional state of the liver is better ascertained from a combination of several liver function tests. Most studies show that in liver disorders impaired glycogenic function as shown by the capacity to metabolize galactose usually comes later than impaired clearance of bromsulphalein, excretion of azorubin-S or bilirubin and synthesis of hippuric acid.

Because these tests are usually designed to throw a maximum load on a liver function, they reveal impaired capacity long before performance has declined sufficiently to produce clinical signs and symptoms. In this way it has become evident that in many diseases, infections and nutritional states, liver function falls off and may play a subtle rôle in the outlook. It has been particularly stressed in Graves' disease and in surgical operations. This is especially significant since it has been found that hepatic function, as revealed clinically and by these tests, may be improved by the administration of glucose and other measures. In general, a normal liver function test is more significant than an abnormal one in a case of suspected liver damage since serious liver damage is not likely to exist in the presence of a normal behavior of these agents in the body. In their application to the differential diagnosis of obstructive and hepatogenous jaundice, the value of the results depends on whether or not the liver is damaged in biliary obstruction. Since the liver is frequently injured in obstructive jaundice, especially when of several weeks duration, the tests are not very helpful except within strict limitations. Under these conditions the finding of normal liver function by these tests is strongly diagnostic of obstructive jaundice. The response of subnormal plasma prothrombin to vitamin K seems to be especially informative in this problem, good response favoring obstruction, poor response hepatitis, and normal response in long-standing biliary jaundice being diagnostic of obstruction. In Graves' disease, although other liver function tests may also be abnormal, the evidence is fairly strong that the galactose tolerance

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test is here best adapted to the diagnostic problems, a normal response again being more significant, virtually ruling out hyperthyroidism in a suspected case.

Dextrose. There is an extensive literature on the use of dextrose in diagnostic tests for disorders of carbohydrate metabolism and some on its application to tests of liver function. There have been numerous variations of the techniques for loading the mechanisms concerned with the metabolism of this sugar in the endeavor to simplify the procedure and render the results more informative and reliable. In the past few years studies have been published using the dextrose tolerance test to explore disorders of carbohydrate metabolism in various diseases and some of these will be briefly reviewed.

In a modification of the 2-dose glucose tolerance test of Exton and Rose, it was found that the most important information is to be obtained from the 1-hour blood sample for the diagnosis of diabetes, and from the 2-hour sample for differentiating degrees of severity (Wayburn and Gray[122]). The 2-dose 1-hour glucose tolerance test often gives results which are in disagreement with the 1-dose method, and the authors in one comparative study conclude that the latter is a more reliable index of diabetes (Langner and Dewees[51]). Patients with a diagnosis of non-diabetic glycosuria, based on a single glucose tolerance test, seem to show a higher than expected incidence of diabetes when reëxamined several years later, signifying the danger of allowing a final decision to rest on a single glucose tolerance test, especially when the results are borderline (Dewees and Langner[24]). A new intravenous glucose tolerance test has been developed for distinguishing between benign glycosuria and diabetes mellitus (Lozner, Winkler, Taylor and Peters[60]). After an intravenous injection of 25 gm. of glucose, a blood sugar level which is greater than 120 mg. per 100 cc. after 2 hours indicates diabetes mellitus, while one less than 100 mg. fairly reliably excludes it. An abnormal oral dextrose tolerance test has often been found in patients with mental disorders. In a comparison of the oral with the intravenous glucose tolerance test in patients with manic-depressive psychosis, the results indicate that the abnormal oral test may be a consequence of delayed absorption, since the intravenous test was normal (Gildea, McLean and Man[27]). The impaired glucose tolerance which is present in patients with pituitary, adrenal, or thyroid disease appears to be related to the fat and carbohydrate content of the diet, and can be altered toward normal by high carbohydrate in the diet. A dextrose tolerance test after a period of high carbohydrate feeding is suggested as particularly important as a means of ascertaining the most favorable period for operation in hyperthyroidism (Greene and Swanson[31]). Marked deviations of the dextrose tolerance tests from the normal are seen in cases of severe burns suggesting, among other things, impaired glycogenic function of the liver (Wolff, Elkinton and Rhoads[132]). Other liver function tests are also abnormal in severe burns. Marginal malnutrition gives rise to a diabetic-like glucose tolerance test and the diagnosis of diabetes should be deferred in such cases until it is found that the curve fails to return to normal following a period of adequate diet (Robinson, Shelton and Smith[99]). It has been generally taken for granted that the glycosuria and delayed utilization of glucose which occur in obesity represent mild forms of diabetes (John[40]). This has been questioned in a study in which it was found that 77% of adult obese hyperglycemic patients showed a return of the glucose tolerance to normal after adequate reduction of body weight (Newburgh[79]). The sug-

gestion is made that obesity impairs the utilization of glucose in a manner that is independent of any disorder of the insulin mechanism.

The rôle of the liver in carbohydrate metabolism is well known and the fact that in severe liver disease there is hypoglycemia is established. While galactose is now usually employed for testing the glycogenic function of the liver, there are many cases of liver disease in which this test has been found normal, but the glucose tolerance test abnormal (Coller and Jackson[20]). A fairly characteristic curve was found in liver disease: normal or low fasting blood sugar, rise above normal in first and second hours, and fall to hypoglycemic levels during the third, fourth and fifth hour. There is the belief that both hyper- and hypoglycemia may at times have their origin in a disturbed glycogenic function of the liver, and that hypoglycemia is frequently a surgical problem, arising from damage to the liver from cholecystitis or cholelithiasis. This may be recognized by the glucose tolerance curve. Others deny the usefulness of the test. In children with catarrhal jaundice, no correlation was observed between the type of curve and other tests of hepatic dysfunction (Pachman[83]). The glucose tolerance curve showed alterations in form and height, and time to return to normal level in patients with gross liver disease, but the results were not sufficiently characteristic or uniform to serve as a basis for the recognition of impaired liver function (Wilson[127]).*

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RADIOLOGY

UNDER THE CHARGE OF

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SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

PULMONARY CYSTS

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In 1687 Bartholinus reported the first recognized case of the disease which has been called "cystic disease of the lung," "cystic degeneration of the lung," or "pulmonary cysts." In 1925 Koontz[10] reviewed the medical literature and found reports of 105 cases of pulmonary cysts. In 1937 Schenck[20] was able to find 381 reported cases. The more frequent recognition of this type of lesion at the present time is due to a great extent to the fact that roentgenologic examination of the thorax now is performed more frequently than it was in the past. In cases in which pulmonary symptoms are due to this condition, the diagnosis can be made only by roentgenographic examination or by exploratory operation. In a relatively large number of cases of pulmonary cysts the patients have no symptoms and it is only by routine roentgenographic examination of the thorax that these lesions are found. Thus roentgenologists who can study the gross character, size, shape and distribution of these cysts should be able to contribute much toward a better understanding of this condition. Conversely the findings of the internists, surgeons and pathologists are of great aid in bringing about a better understanding of these cysts by roentgenologists. It is certain that no one should realize more clearly than the roentgenologist the complexity of the problems involved in trying to understand this perplexing condition.

Some writers, especially Peirce and Dirkse,[16] have objected to the term "cyst" to designate this lesion. They claim that cysts are hollow organs, bladders or sacs which contain liquid secretion, parasitic larvæ or morbid

matter. Thus they felt that only those cysts of the lung which are or have been filled with fluid properly should be called "cysts." This is arguable even on etymologic grounds and relatively unimportant. At any rate by common practice the term "cyst" has for many years been applied to certain air-filled cavities in the lungs, and it is neither possible nor desirable to change the terminology in this respect. When the exact nature of the pulmonary cysts is understood, as is the case in some instances, a more specific term may be substituted, but when the pathogenesis is not understood, the general term "cyst" is still preferable. Some authors have used the term "air cyst" to designate cysts that do not contain fluid.

As pulmonary cysts are seen by the roentgenologist first, it would perhaps be best to consider the appearance of these lesions and their distribution as seen in roentgenograms of the thorax. It would be possible in this way to subdivide them according to their size, shape, number and distribution in the lung. Sellors'[21] classification is quite suitable for this purpose:

1. Solitary cysts—almost invariably of large size.

(*a*) Huge "balloon" or "distention" cysts, which when they occur in infants cause gross pressure signs and often death.

(*b*) Smaller cysts about the size of an orange. These often remain "silent" unless infected.

2. Multiple cysts of variable size.

(*a*) Medium sized, in groups of two or three, close to the root of the lung on occasions. They vary in size from that of a cherry to that of a golf ball. They usually do not cause symptoms.

(*b*) Small cysts the size of a currant or a cherry.

Multiple cysts may also be divided as:

1. Those which follow a set distribution and which usually are lobar in character. These cysts are uniform in size; they resemble saccular bronchiectasis. Some of these have been called "honey-comb" lung.

2. Diffuse or scattered lesions with cysts of inconstant size: (*a*) localized patchy distribution; (*b*) confined to one lung only; (*c*) scattered through both lungs.

There may be objections to this classification but it is the only one found which is based objectively on the morphology and distribution of the cysts. Certainly, one should not attempt to classify these cysts according to their cause until the great variation in the character of the pulmonary cysts is considered. In other words, one should consider etiologic factors that apply to each type of pulmonary cyst rather than discuss pulmonary cysts as though they comprised a homogeneous group. The failure of most investigators to do this makes a discussion of pathogenesis very difficult.

At first it was thought that all pulmonary cysts were congenital. Both Koontz[10] and Schenck[20] expressed this opinion. Anspach and Wolman,[1] who studied pulmonary cysts in infants, regarded them as congenital. Sauerbruch,[19] who studied bronchiectasis in children, found that 80% of these cysts were congenital in origin and did not cause inflammatory changes in the lung. This congenital bronchiectasis he termed as cystic bronchial disease. Sellors mentioned the similarity between multiple congenital cysts and congenital bronchiectasis. Many other authors have supported the congenital origin of pulmonary cysts.

It would not be suitable here to mention all the theories in support of the congenital origin of pulmonary cysts, which have been well reviewed

by Willis and Almeyda,[28] Stanford and Nalle,[24] and Gruenfeld and Gray;[7] especially to be recommended is the paper by Sellors. Some of the theories of the congenital origin, however, will be considered briefly. Anspach and Wolman[1] suggested three ways in which congenital cysts may start. A large cyst may be preformed but collapsed at birth; then it may become distended at the first inspiration. Cysts may develop from small congenital bronchiectatic dilatations which enlarge in postnatal life as the result of stenosis of their orifices. A large air cyst may occur primarily as a large sac which is filled with fluid. The fluid is evacuated spontaneously into the bronchus by rupture of the cyst, which then becomes filled with air.

Anspach and Wolman found pulmonary enterogenous cysts in infants, as did Ward and Krahl.[26] These enterogenous cysts are, of course, congenital. They are very rare, but must be considered when a cyst which contains fluid and progressively increases in size is found in a newborn infant. In 1 case reported by Ward and Krahl, a spontaneous pneumothorax developed as the result of the rupture of an enterogenous pulmonary cyst.

Müller,[14] in 1928, in a review of the theories of the pathogenesis of pulmonary cysts, was of the opinion that a bronchiolar bud becomes arrested in its growth before attaining the stage of a hollow tube and that, at a subsequent date, the terminal part begins to grow and forms a closed sac into which fluid is secreted by the lining epithelial cells. He quoted Simpkins, Crosswell and King, and Harris in support of his theory.

These concepts of the congenital origin of pulmonary cysts seem to apply best to certain types which have been described by Sellors. It does seem that some of the "balloon" or "distention" cysts found in newborn infants are congenital in origin. The solitary "smaller cysts which are about the size of an orange," as described by Sellors, also often seem to be congenital. These are usually filled with fluid until they rupture into a bronchus. After this, they contain varying amounts of fluid which may be evacuated at intervals. These solitary congenital cysts are originally, at least, lined with ciliated columnar epithelium and there may be regions of squamous metaplasia. The walls of the cysts may contain glands, smooth muscle, elastic tissue, lymph follicles, and cartilage. Infection may destroy the epithelium. These cysts are often traversed by strands of fibrous tissue.

There is considerable evidence to support the idea that many pulmonary cysts should be considered "developmental" rather than "congenital." According to Miller,[13] the studies of Broman, Willson, Strukow, and Stefko indicate that the permanent pulmonary parenchyma of the adult develops only after birth and that this development requires from 3 to 14 years; the average time required is about 7 years. Miller expressed the opinion that disturbance in the development of the lung produces both congenital bronchiectasis and congenital cystic lung. He said that arrest of development, whether prenatal or postnatal, means the persistence of the primitive infantile type of lung from childhood into adolescence. The bronchi in such a lung do not branch normally; they become stretched and distended, and develop into bronchiectatic or cystic structures, depending on whether they remain patent or become shut off at their proximal end. Of course, this disturbance in development may result from extrinsic causes; in some cases it is undoubtedly due to pulmonary infection early in life. This concept of the pathogenesis of those types of

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pulmonary cysts which resemble or are associated with congenital cystic bronchiectasis seems quite logical.

Willis and Almeyda expressed the opinion that the pulmonary cysts may be either congenital or acquired but they preferred the term "developmental" since they believed that there is usually an underlying weakness of the bronchial or alveolar structures. Examples of cystic lung in cases of familial tuberous sclerosis have been reported by Berg and Zachrisson,[3] and Berg and Vejlens,[2] and these pulmonary changes seem to be due to some developmental disturbance. Stanford and Nalle reported a case of emphysematous type of cystic lung which appears to be due to a deficiency in the connective tissue stroma. Koontz quoted Humbert as saying that there are some instances in which there is no deformity at birth but in which there is some defect in the structure of the bronchial walls which later results in malformation. Gruenfeld and Gray[7] describe how they think multiple cysts can result from developmental variation. They also said that the following theories have been advanced to explain the congenital or developmental nature of pulmonary cysts:

1. Primary agenesis of finer ducts and alveoli (Wolman, Huckel, Grawitz, DeLange). The cysts are passive dilatations of originally normal air ducts.

2. Neoplastic hyperplasia of the bronchial tree, "cystic bronchoadenoma" (Stoerk, Wermbter, Alth).

3. Hydropic dilatation of congenitally malformed lymph spaces (Virchow, Klebs, quoted by DeLange).

4. Congenital deficiency of elastic tissue (von Hauseman, Dey).

5. Secondary dilatation of air containing ducts due to persistence of congenital atelectasis (Hiller, Sauerbruch).

6. Fetal bronchopneumonia, mostly syphilitic, leading to stasis of bronchi (Balzer) or to arrested alveolar development (Sandoy).

7. Lobular pneumonia or pneumonitis in childhood, disturbing the differentiation of the pulmonary parenchyma (Miller).

8. Uncoördinated excessive growth of the pulmonary stroma, interfering with the proliferation of the parenchyma, a hamartoma in the sense of Albrecht (Kimla).

9. Stenosis of short segments of the air ducts developing in the prenatal or postnatal period (Eloesser).

With reference to the second and sixth theories, it may be pointed out that, according to the consensus of writers, pulmonary cysts are rarely neoplastic or due to congenital syphilis.

Recently, there has been considerable support given to the concept that pulmonary cysts are acquired and not congenital. Peirce[15] and Peirce and Dirkse,[16] who deserve much credit for stimulating thought in this direction, emphasized that pulmonary cysts are frequently the sequelæ of bronchitis and bronchopneumonia. They expressed the opinion that although congenital cysts may occur they are rare, and that in a very large number of cases the cysts are not congenital. They subdivided cystic pulmonary disease as follows:

I. True congenital pulmonary cyst or cysts.
II. (*a*) Chronic interstitial pneumonitis with emphysema; (*b*) chronic bullous emphysema.
III. Cystic bronchiectasis.
IV. Pulmonary pneumatocele (localized alveolar or lobular ectasia).

Pulmonary pneumatocele starts as an acute lobular emphysema associated with lobular pneumonia or bronchitis. A persistent check-valve

obstructing the lumen of the bronchus is thought to be due either to non-resolution of the initial inflammation of the bronchus or to a subsequent distortion of the dilated air-spaces. This check-valve type of obstruction of the bronchus has been well described by Jackson.[8] Cheney and Garland[6] gave support to the theory that pulmonary cysts are acquired by demonstrating that serial roentgenograms of patients recovering from various inflammatory disease of the lungs, especially pneumonia, disclose an astonishing number of bizarre cystlike lesions. Some of the lesions disappear spontaneously but many remain unchanged. Some increase in size and eventually occupy an entire lobe or even a whole lung. These lesions were called "pneumocysts" by Cheney and Garland,[6] who said that they represent a bullous-emphysema phase of healing. Caffey[5] found that in infants with pneumonia there developed, at times, lesions which looked like abscesses, tuberculous cavities or congenital cysts of the lung but which were in reality due to a regional obstructive pulmonary emphysema. They were sometimes multiple. So-called balloon cysts were encountered as the result of this type of regional obstructive pulmonary emphysema, which is a term that can be considered synonymous with pneumatocele. They usually disappeared spontaneously. Some of these acquired lesions greatly resembled solitary congenital cysts.

Maier[11] thought that many pulmonary cysts are acquired, although he recognized that congenital cysts are not rare. He also emphasized the importance of recognizing pneumatoceles which follow interstitial pneumonitis. These may disappear more quickly in infants and children than in adults. He found that in children pneumatoceles may attain huge size. Some pneumatoceles remained only a few weeks while others persisted and fluctuated in size for months or years without producing symptoms. He emphasized the importance of distinguishing pneumatoceles from emphysematous bullæ since a bulla does not disappear but tends to increase in size slowly, whereas a pneumatocele may rapidly increase or diminish in size and not infrequently will disappear completely and spontaneously. However, if an emphysematous bulla has a constant increase in intracavitary pressure he would call it a pneumatocele, even though it occurred in an emphysematous lung.

There may be difficulty in distinguishing pneumatocele from abscess of the lung. According to Maier, either pneumatocele or abscess may become inflated due to a check-valve action in the bronchus. This inflation of an abscess occurs most frequently in children and infants. Maier emphasized that a pulmonary abscess may persist after the infection has subsided. This is usually due to fibrosis of the surrounding lung but may be due to ingrowth of epithelium. Such an abscess might be confused with an infected cyst.

As Maier has emphasized, emphysematous bullæ are an advanced form of emphysema and should not be called cysts. Differential diagnosis is not always easy, however. Weaver and von Haam[27] have discussed the mechanism of the development of emphysematous regions which resemble cysts. Caffey has noted the similarity between bullous emphysema and annular cysts. Maier said that if an intrapulmonary air cyst is produced chiefly or entirely by disruption of intra-alveolar septa and if there is little or no check-valve, it is not a pneumatocele but a bullæ; however, if the size of the cavity is large, owing to hyperinflation of an originally small cavity, it is a pneumatocele. Maier mentioned that bullæ may be difficult to distinguish from pneumothorax. Pulmonary blebs are acute and are usually easily distinguished, according to Maier.

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Maier objected to the use of the term "pulmonary cyst" without qualifications. He felt that attempts should be made to distinguish the various types if possible. He said that the formation of a cavity in the lung is a developmental abnormality, is due to destruction of pulmonary tissue by an inflammatory process, is the result of hyperinflation of a small defect in the pulmonary parenchyma, or is due to a combination of these processes. The following is Maier's classification of pulmonary cysts:

I. Non-parasitic cysts and cystlike cavities.

1. Congenital pulmonary cavities.
2. Cystic bronchiectasis.
3. Acquired intrapulmonary cavities originally produced by destruction of pulmonary tissue. The cavity may or may not be epithelialized.
4. Pneumatocele: non-epithelialized positive pressure cavities produced by hyperinflation of a defect in the pulmonary parenchyma resulting from pulmonary infection.
5. Emphysematous bullæ: non-epithelialized pulmonary cavities, produced chiefly by disruption of intra-alveolar septa.
6. Pulmonary blebs: localized collections of air within the pulmonary interstitial tissue.

II. Parasitic cysts.

This classification is very satisfactory. The great difficulty is that it frequently is almost impossible to decide definitely by roentgenographic and clinical methods just how a certain cyst should be classified. The reason for this was well expressed by Smith,[23] who said: "One may hazard the opinion that though the majority of cases are due to some embryologic defect, many are acquired as the result of damage to the bronchi and lungs by previous infection, inhalation of foreign material, or trauma. Given a lung with a developmental fault, or with a residuum of injury of acquired factors, add the interplay of the normal forces which have to do with the mechanics of respiration, namely, traction, pressure effects and drainage, and add to these insults from repeated infections, then there is likely to result a varied pathologic picture in which may be found entrapped air, pocketed fluid, fibrotic formations, pneumonitis, distended and deformed bronchi, and perhaps not rarely a complicating pneumothorax."

Anspach and Wolman[1] made an important point when they said: "Once a cyst has formed its behavior is determined largely by mechanical and accidental influences, such as capsular strength, proximity of adjacent air passages, plasticity of surrounding lung tissue, and the presence or absence of complicating respiratory infections, rather than by its embryogenesis or history of its lining." This is well shown when so-called balloon cysts are considered. Many of these cysts that occurred in infants and were described by Anspach and Wolman appeared to be congenital. However, Caffey[5] found that some balloon cysts in infants apparently were the result of an inflammatory process and he called them "regional obstructive pulmonary emphysema." Maier,[11] Kirklin,[9] Brown and Brock,[4] and Cheney and Garland[6] have reported balloon cysts which probably developed in adult life and which may be called "giant pneumatoceles." The important thing is not whether these were congenital or acquired. The only matter of real importance is that these lesions have a check-valve mechanism in the communicating bronchus which causes the cysts to expand progressively and thus may result in death from respiratory embarrassment.

Rigler[17] has briefly summarized very well the ways in which pulmonary cysts may produce symptoms. These are as follows:

1. There may be loss of lung tissue owing to expansion of the cyst, compression of the remaining lung, and displacement of the mediastinum. Diminished vital capacity may embarrass respiration, especially in children but perhaps also in adults.
2. Infected cysts may cause symptoms of pulmonary suppuration.
3. There may be enlargement of the right side of the heart and cardiac failure.

Tyson[25] has found that patients who have solitary pulmonary cysts usually seek relief because of infection or alteration of the mechanical air exchange through a connecting bronchus. Rupture may occur in either case. These infected cysts are often confused with abscesses. The complications occurring in his cases were: (1) infection of the cyst without rupture; (2) infection with rupture and formation of a pyopneumothorax; (3) progressive expansion of the cyst after subsidence of infection; (4) rupture without infection but due to ball-valve effect and formation of tension pneumothorax; (5) rupture of the cyst with discharge of sterile fluid into the pleural cavity.

The surgical treatment of these conditions is not within the scope of this paper, but certain aspects of the surgical treatment are very important and should be considered.

Rigler,[18] Maier,[11] Maier and Haight,[12] and Tyson[25] have shown how an infected cyst may simulate an empyema; this is especially true if the cyst has ruptured into the pleural space. With an infected pulmonary cyst there is not the pleural reaction that one would expect with empyema. The shape of the cyst, if it has not ruptured, may make its distinction from empyema possible by roentgenographic examination.

It is important to distinguish congenital cysts from non-epithelialized intrapulmonary cavities, such as a pneumatocele, since the latter frequently will disappear spontaneously. If empyema results from the rupture of a congenital cyst it is not sufficient merely to drain the empyema cavity since the epithelialized cyst will not collapse and must be removed. This applies also to infected pulmonary cysts which have not ruptured but have nevertheless been confused with empyema. If empyema does not respond to the usual surgical procedures, one should consider the possibility of a congenital pulmonary cyst. Congenital cysts are lined with columnar epithelium in contrast with the alveolar epithelium, squamous metaplasia or inflammatory tissue which lines bronchiectatic cavities or acquired cysts. The strands of tissue traversing a congenital cyst may be visible in the roentgenogram. The distorted elements of the bronchial wall are often found in the walls of a congenital cyst. Thus biopsy in the course of surgical drainage of an empyema cavity often will disclose the nature of the lesion. If it is a congenital cyst its surgical removal will be necessary. Old abscess cavities of the lung may be lined by bronchial epithelium which has grown in from a bronchus. In this case, the lesion would simulate a congenital cyst but this would make little difference since surgical removal of the abscess would be necessary. Lack of anthracotic pigment within the cyst and in the vicinity of the walls of the cyst has been given by Schenck and Koontz as an indication of lack of function of the tissue and of the congenital origin of the cyst. This might at times be an important point, since the epithelial lining of a congenital cyst sometimes is destroyed by infection.

A tension pneumothorax should be distinguished from a giant pneumatocele which virtually fills the entire lung. Around such a large pneumatocele there can usually be seen some compressed pulmonary tissue,

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especially in the apex of the lung and in the costophrenic angle. The hilar shadows are not prominent when there is a balloon cyst whereas in a tension pneumothorax the collapsed lung forms a prominence at the hilus.

It is true that at times the bronchial communication of an air containing cyst cannot be found when the specimen is examined. This is especially true of balloon cysts. Consideration of the physiology of the lung makes it evident that there must be such a communication even though this cannot be seen during examination of the specimen. Anspach and Wolman said that, probably, the communicating bronchiole, entering the cavity by an angular tortuous course, is difficult to demonstrate and by its nature may act as a valve and allow the entrance of air but not its exit.

The use of bronchography with iodized oil in cases of cystic lung is not considered to be of much assistance according to most authors. In most cases the cysts fail to become filled with the oil. Singer[22] has used iodized oil to distinguish solitary congenital cyst from empyema. He injected the iodized oil directly into the cavity and then made roentgenograms at many angles and even with the patient upside down. Maier thought bronchography might be of some value in distinguishing a cyst from empyema.

Since cystic bronchiectasis and certain types of pulmonary cysts are very difficult to distinguish and since an infected cyst of the lung would probably require surgical treatment similar to that used for relief of bronchiectasis, it seems that in cases of cystic lung bronchography would be indicated to show the extent and character of the lesion. Solitary pulmonary cysts which are infected are often found to be associated with adjacent bronchiectasis; therefore, bronchography would be indicated to determine the extent and site of the bronchiectasis.

Cavernous bronchogenic carcinoma may have an appearance which roentgenographically is identical with that of an infected solitary pulmonary cyst. Bronchoscopic examination and biopsy will often reveal the presence of carcinoma.

Conclusions. 1. In many cases of pulmonary cysts the pathogenesis cannot be definitely determined.

2. Some pulmonary cysts are congenital in origin.

3. Some pulmonary cysts may be best regarded as "developmental" in origin.

4. Some pulmonary cysts are acquired, usually as the result of pulmonary infection.

5. At times, acquired factors probably cause the development of pulmonary cysts by distorting "developmental" processes.

6. Lesions that may not actually be pulmonary cysts may at times be distinguished with difficulty. This applies especially to emphysema and bronchiectasis.

7. The importance of distinguishing empyema from an infected pulmonary cyst must be remembered.

8. Very large balloon cysts must be distinguished from tension pneumothorax.

9. An infected cyst of the lung should be distinguished from pulmonary abscess, tuberculous cavitation and cavernous bronchogenic carcinoma.

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PHYSIOLOGY

THE CLINICAL SIGNIFICANCE OF THE CAROTID AND AORTIC BODIES

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THE recent discovery of the functions of the carotid and aortic bodies constitutes a major advance in physiology. Although certain details remain to be reinvestigated and reëvaluated, there is enough general agreement among physiologists on fundamental concepts to warrant an interpretation of the available data for clinicians. This review will emphasize the *clinical* significance of the carotid and aortic bodies and will merely outline the historical development and anatomic characteristics of these cell groups. Those desiring more detailed information are referred to review articles by several of the original investigators in the field.[6,26,30,50]

Description of the carotid bodies dates back to 1743, but it was not until 1902 that Biedl and Wiesel[8] reported a structure which we recognize today as the aortic body. For years these tissues were variously regarded as glands of internal secretion, chromaffin bodies, paraganglia, or cavernous vascular structures. In 1928 de Castro[22] shrewdly suggested that on the basis of its peculiar histologic appearance the carotid body might represent a special sense organ capable of perceiving changes in the chemical composition of the arterial blood. This was conclusively demonstrated by Heymans in 1930.[29] A similar function was attributed to the aortic body by Comroe[16] in 1939.

A. **Physiology.** To avoid confusion, one important fact must be established at the outset. The sensory receptors of the carotid and aortic bodies are anatomically adjacent to other receptors which have a some-

what similar name, *i. e.*, the receptors of the carotid sinus and aortic arch. It is unfortunate that the identity of these structures is so frequently confused for, despite their proximity, they have quite different functions. The receptors of the carotid and aortic bodies respond to changes in the *chemical constitution* of arterial blood and should be regarded as *chemoreceptors*. The receptors of the carotid sinus and aortic arch respond to alterations in *arterial pressure* and should be referred to as *pressoreceptors*. Although both groups exert important effects upon respiration and circulation, the results of stimulation of each are diametrically opposed.

It is now well established that stimulation of the sensory receptors of the carotid and aortic bodies leads to increased activity of certain portions of the central nervous system. A first concern must therefore be a consideration of what activates the receptors, together with a discussion of the effects of such activation.

The Stimuli. The chemoreceptors are stimulated by certain changes in the composition of arterial blood:

(*a*) Decrease in arterial oxygen tension. The distinction between oxygen content and oxygen tension (pressure) is often poorly understood Oxygen content of arterial blood refers to the amount of oxygen in chemical combination with hemoglobin (normally about 19 to 20 cc. per 100 cc. blood) plus the oxygen physically dissolved in the plasma (about 0.2 cc. per 100 cc. blood). Oxygen tension (pressure) of arterial blood refers to the pressure which the physically dissolved oxygen exerts in the plasma.

The response of the chemoreceptors to a lowered oxygen tension is prompt, intense and prolonged, and represents the organism's chief defense mechanism against anoxia. Whatever resistance the intact individual has against anoxia is due to a flow of afferent impulses from these peripheral receptors, and is not due to a stimulant action directly upon the medullary centers as was formerly believed. This reaction to oxygen deficit constitutes the most important physiologic property of the carotid and aortic bodies.

(*b*) Increase in acidity.

(*c*) Increase in carbon dioxide tension.

(*d*) Increase in blood temperature.

(*e*) Certain drugs: cyanides, sulfides, nicotine, lobeline, papaverine, etc.

The Response. Increased chemoreceptor activity is evidenced particularly by the response of the respiratory and vasomotor centers. Stimulation of the chemoreceptors results in:

(*a*) Increase in respiratory rate, depth and minute volume.

(*b*) Increase in sympathetic nervous system activity: increase in pulse rate, arterial blood pressure, vasoconstrictor tone, and liberation of adrenalin.

(*c*) Increase in cerebral cortical activity. Evidence obtained from dogs indicates that excessive stimulation of the carotid and aortic bodies produces cortical stimulation which may progress to convulsions.[47,48] It is possible, therefore, that afferent impulses from these end organs may play a rôle in maintaining cortical function in the face of derangements such as narcosis or anoxia (see page 689). The restlessness of anoxia may be due in part to this factor.

The responses noted above can be maintained for relatively long periods of time.[13] These receptors are evidently rugged structures which can continue to discharge impulses under conditions which produce marked depression of the central nervous system. This has led Schmidt to regard

the carotid and aortic bodies as the "ultimum moriens" of the respiratory system.[49]

The Rôle of the Chemoreceptors in Normal Man. While the chemoreceptors are important to man during such emergencies as anoxia and acidosis, they appear to have no important function that is demonstrable under normal conditions. Extirpation or denervation of the carotid and aortic bodies in dogs produces no lasting change in the rate, depth, or minute volume of respiration, in B.P.,* pulse, arterial oxygen or carbon dioxide tension or pH. While breathing room air, they behave entirely normally.[59]

Surgical removal of the chemoreceptors has not been performed in man, but one can estimate the degree of their activity by a "physiologic denervation." The inhalation of 100% oxygen probably accomplishes such a denervation for the following reason: If the carotid and aortic bodies of a normal man breathing room air were activated by the oxygen tension of 97 mm. Hg existing in arterial blood,[20] this should be a factor in the maintenance of normal respiration and circulation. Inhalation of 100% oxygen, by raising arterial oxygen tension to 670 mm. Hg should abolish this chemoreceptor activity. Since the major function of the chemoreceptors is the response to lowered oxygen tension, removal of this component of chemoreceptor activity should depress respiration and circulation.† However, inhalation of 100% O_2 rarely decreases respiration of normal men and usually increases it about 10%.[56,59]‡ This indicates that there is no demonstrable tonic chemoreceptor activity in normal man.

However, during certain deviations from normality chemoreceptor function is of undoubted importance. The rôle of the carotid and aortic bodies under such conditions forms the basis for this review. Before discussing their clinical significance, however, the derivation and structural characteristics of these end organs will be sketched briefly.

Embryology. According to Boyd[9] the embryologic significance of the carotid body is found in its connection with structures of the third branchial arch. Its primordium is mesoderm of this arch, and its earliest connections are with the artery of this arch and the ectoderm of the glossopharyngeal nerve. The aortic body has a similar origin from the fourth branchial arch and the vagus nerve. There is therefore a clearly defined combination of vascular and neural elements from the outset. The fifth branchial arch is represented in the fetus of some animals by a pulmonary body, but this rarely persists in adult life. Other cell groups (such as the abdominal paraganglia and coccygeal bodies) may respond to chemical changes in the arterial blood; Hollinshead's experiments, which attribute a function of this type to the abdominal paraganglia in mice and rats are of interest in this regard and should be repeated.[31]

* Since the nerve fibers from the carotid sinus pressure receptors and from the carotid body chemoreceptors join and enter the glossopharyngeal nerve, any attempt to block, denervate or extirpate the carotid bodies (in dog or in man) will result in loss of function of the carotid sinuses. This should result in "carotid sinus hypertension." However, the aortic arch pressure receptors can assume the function of the carotid sinuses and maintain a normal level of blood pressure. Since it has been found possible to denervate the aortic body in the dog without damage to the aortic pressure receptors,[50] these dogs maintained a normal blood pressure.

† Oxygen inhalation, of course, does not remove whatever tonic discharge might result from receptors activated by the normal acidity, carbon dioxide tension, and temperature of arterial blood, but there is little evidence to indicate that such tonic activity is important.

‡ It is interesting to note that a similar "physiologic denervation" in normal, unanesthetized dogs depresses respiration by 10 to 30% for a period of 1 to 3 minutes, indicative of a minor degree of tonic chemoreceptor discharge. This species difference emphasizes the undesirability of transferri..g the results of animal experimentation to man.

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The occurrence of the carotid and aortic bodies in relation to branchial arches assumes more significance as one considers the respiratory mechanisms of fish.[36] Fish take up oxygen from water as it flows through the branchial (gill) system. This branchial respiration in aquatic animals is regulated by the tension of oxygen in the water, a decreased oxygen tension tending to stimulate respiration.[37] It seems probable, therefore, that the carotid and aortic bodies in higher forms of life represent the survival of structures which control respiration in water-breathing animals.

Gross Anatomy. A carotid body is situated close to the bifurcation of each common carotid artery. In man the carotid body is about 2 to 3 mm. in its longest diameter and can be demonstrated grossly only with difficulty. Its blood supply is derived from the external carotid artery and its ascending pharyngeal and occipital branches. The nerve supply is the carotid branch of the glossopharyngeal or ninth cranial nerve.

The anatomy of the aortic body in man is less clearly understood, although J. D. Boyd[9] describes two structures which he regards as homologous to carotid bodies. One of these is found near the innominate artery, usually on its lateral aspect; fibers from the right vagus nerve can be traced to it. The other is situated on the anterolateral aspect of the left portion of the aortic arch; this is closely associated with the left vagus nerve. In the dog and cat, the aortic bodies lie between the ascending aorta and the pulmonary artery and receive their blood supply either from the aorta directly or from the coronary arteries. As a rule, their nerve fibers enter the vagi along with the recurrent laryngeal nerve.[16]

Histology. The structure of these bodies is unusual in that the afferent arteries open directly into sinusoidal spaces lined only with endothelium. The cells are arranged in the form of thin anastomosing cords or small cell groups separated from each other, so that each cell is in close relation to the blood stream.[9] There is a rich nerve supply and an intimate relationship between the nerve endings in the cells and the blood stream. This is of the utmost physiologic significance, creating as it does an optimal situation for reaction to changes in the chemical constitution of the blood.

A knowledge of the histologic structure of the carotid body is also of importance clinically, in that it aids in the diagnosis of carotid body tumors. More than 250 tumors of the carotid body have been reported and these have been referred to as endotheliomas, peritheliomas, neuroblastomas, sympathoblastomas, angiomas, fibroangiomas, sympathetic nevi, adenomas, angiosarcomas, perithelial hemangiomas and paraganglionomas.[27] This confused terminology can undoubtedly be explained on the basis of the threefold nature of the carotid body, composed as it is of vascular, neural and fibrous tissues. Tumors can arise from any or all of these three tissues, the histologic picture being different in each. As far as we are aware, no tumor formation has yet been described in the aortic body though some mediastinal tumors may conceivably arise from this structure.

B. **Clinical Importance of the Chemoreceptors.** ANOXIA. There is no doubt that man may respond in striking fashion to severe anoxia (see page 682). As has been pointed out, most or all of this response originates in chemoreceptor reflexes. The latter has been demonstrated in dogs by (*a*) removal or denervation of the chemoreceptors during severe anoxia (in which case respiration and circulation are depressed) and (*b*) production of anoxia in animals previously denervated (in which case the usual prompt stimulation of respiration and circulation is lacking).

This marked response to severe anoxia and the demonstration of the rôle of the chemoreceptors in anoxia has led some physiologists to believe that the chemoreceptors are of utmost importance in all anoxic states. This is certainly not true. The chemoreceptors are very important, sometimes vitally important, in certain anoxic conditions. In others, they are active but are non-essential to the maintenance of circulation and respiration, and in still other anoxic states, they are not involved at all.

In order to clarify this important point, a classification of clinical anoxia will be introduced which differs from that of Barcroft.[4] We shall divide anoxic states into only two groups: those in which the *arterial oxygen tension* is *normal* and those in which it is *low*. This division is a logical one, since the stimulus activating the chemoreceptors is a decrease in the oxygen tension of the arterial blood rather than a decrease in oxygen content of whole blood.

I. Anoxic Conditions With A *NORMAL* Arterial Oxygen Tension. Clinical conditions fitting this category are: (*a*)carbon monoxide poisoning, in which anoxia is produced by reason of the greater affinity of hemoglobin for CO than for O_2, though arterial oxygen tension is normal; (*b*) methemoglobin formation, as in nitrite, sulfanilamide, acetanilid poisoning, or sulfhemoglobin formation in which functioning hemoglobin is reduced though arterial oxygen tension is normal; (*c*) anemia, in which the quantity of hemoglobin is decreased but plasma O_2 tension is normal; and (*d*) certain types of peripheral circulatory failure in which tissue cells may be supplied with less blood per unit time though each unit of blood is well oxygenated (*e. g.*, shock).

Carbon monoxide poisoning illustrates certain principles applicable to this whole group. As indicated previously, because of the great affinity of hemoglobin for CO as compared with O_2 (210:1) only 1/210 as much CO as O_2 is needed in inspired air to enable carbon monoxide to compete on even terms with O_2 and so produce 50% HbCO and 50% HbO_2. Thus the addition of only 0.1% CO to inspired air will produce 50% HbCO and serious poisoning though the oxygen in inspired air will be reduced from 20.93% to 20.91% (a reduction of only 0.15 mm. Hg pO_2—from 159 to 158.85 mm. Hg). Since there has been only an infinitesimal reduction in oxygen *tension*, one would expect minimal or no chemoreceptor activity. However, at the same time, there is a marked reduction in arterial O_2 *content* (to 50% HbO_2). If anoxia were capable of stimulating the chemoreceptors or respiratory center by virtue of a reduction of HbO_2, one would expect to see a definite augmentation of circulation and respiration.

This question was put to a direct test by Chiodi *et al.*,[14] who exposed 4 unanesthetized men to prolonged inhalations of 0.15 to 0.35% carbon monoxide in air. In 13 experiments the HbCO produced was between 30 to 40%, in 9 experiments it was between 40 to 50% and in 1 experiment the HbCO attained was 52%. Nevertheless in none of these 23 experiments was there any change in the minute volume of respiration. Therefore it is evident that the chemoreceptors do not respond to a diminution in the % HbO_2 in the arterial blood. Similar results were obtained in dogs by Comroe and Schmidt.[18]

In the human experiments there was no circulatory stimulation until the HbCO rose above 30%; then increases in cardiac output (25 to 30%) and in pulse rate occurred. Since simultaneous increases in blood pressure did not occur, the vasomotor center was probably not stimulated by anoxia; more likely the response was secondary to local peripheral vasodilation caused by tissue anoxia.

This work suggests several important clinical implications: (1) The clinician must not expect a patient moderately or severely poisoned with carbon monoxide to be dyspneic or hyperpneic despite the existence of a dangerous degree of tissue anoxia; it is this feature (along with the presence of a cherry red color—*i. e.*, lack of cyanosis) that makes carbon monoxide one of the most insidious of all poisons. Similarly, in moderate

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degrees of anemia, methemoglobin formation, and so on, dyspnea will be lacking. (2) Anoxia stimulates respiration and circulation in man only by reflexes arising in the chemoreceptors. If the chemoreceptors are not stimulated (arterial oxygen tension maintained normal), no respiratory stimulation can be expected from anoxia even though the amount of oxygen carried by the hemoglobin has fallen to 48%. Put in other words, anoxia *does not stimulate the respiratory center directly.** In fact, Chiodi *et al.*[14] obtained some evidence that anoxia may depress the respiratory center by its direct action: in 2 subjects, inhalation of 2 to 5% CO_2 in air produced 11 to 13% more respiratory stimulation in the normal state than during the period of anoxia caused by CO.†

II. Anoxic Conditions With A *SUBNORMAL* Oxygen Tension. This group, in which arterial oxygen tension and, as a rule, arterial oxygen saturation are both reduced, includes the great majority of clinical types of anoxia: conditions associated with primary depression of respiration (morphine or barbiturate poisoning, anesthesia produced by pentothal, evipal, avertin, morphine, and so on), breathing of gases with a subnormal oxygen tension (as at high altitudes, or in decompression chambers, during nitrous oxide or ethylene anesthesia, or during nitrogen inhalations in the treatment of dementia precox), and conditions associated with inadequate gas exchange in the pulmonary alveoli (such as pneumonia, atelectasis, pneumothorax, hydrothorax, pulmonary edema, cardiac decompensation, emphysema, asthma, and so on).

1. *Anoxia Associated With Primary Depression of the Respiratory Center.* Marshall and Rosenfeld[39] have shown that narcotics depress the respiratory center in the medulla as judged by the inability of these cells to respond to CO_2. Since extreme sensitivity to CO_2 is a dominant factor in the control of normal respiration, one might expect that narcosis would be followed by a decreased minute volume of breathing and the development of arterial anoxemia. This sequence of events occurs during narcotic poisoning and during administration of many anesthetics.

(*a*) *Narcotic Poisoning.* If an individual has received an overdose of an opiate or a barbituric acid derivative, minute volume of breathing is reduced below normal, oxygen tension in the arterial blood falls and the chemoreceptors of the carotid and aortic bodies are activated. As narcosis becomes more profound, reflexes from the chemoreceptors assume greater

* It may be wondered how the same arterial blood is capable of producing cerebral anoxia without producing chemoreceptor anoxia. This may be satisfactorily explained by referring again to the unusual vascularity of the chemoreceptors which provides these bodies with arterial blood far in excess of their metabolic needs so that dissolved plasma O_2 alone is adequate for metabolic needs. In the brain, the blood flow is more closely adjusted to the oxygen needs of the tissue, and consequently a decrease in O_2 content (without a compensatory increase in blood flow) will lead to an oxygen deficiency of this rapidly metabolizing tissue.

† The fact that anoxia is purely depressant to respiration and circulation has been established previously by numerous investigators using anesthetized dogs with denervated chemoreceptors. However, different results have been obtained if the denervated dogs are unanesthetized or very lightly anesthetized. Under such conditions, anoxia produces the expected depression of respiration, but this is followed in 2 to 5 minutes by an increase above normal.[59] This increased minute volume, however, is accomplished entirely by an increase in rate; depth being normal or decreased. Since the intact animal responds to anoxia chiefly by an increased depth of breathing, the reaction of the denervated dog represents a distinctly abnormal respiratory pattern. This response differs from that of man, and a species difference again appears to be involved. The presence of other as yet unidentified chemoreceptors in the dog (abdominal paraganglia, coccygeal body) must be ruled out before a definite statement can be made that the respiratory center, even in the dog, is capable of being stimulated directly by anoxia.

and greater importance. The chemoreceptors are stimulated more strongly by increasing anoxia at the same time that the respiratory center is being depressed by the narcotic. When a sufficient degree of central depression has been produced, these afferent impulses may be *entirely* responsible for the maintenance of respiration and perhaps circulation. The control of these vital functions has shifted, in other words, from a delicate sensitive central regulation by CO_2 to a more primitive, resistant, peripheral reflex drive by oxygen lack.

To the physician examining such an individual, this state of affairs may not be evident, unless two diagnostic and prognostic tests are made: (1) Inhalation of 5 to 10% CO_2 *in air*. This will indicate the presence of central depression, since the rate and depth of breathing will not increase, and may even diminish because of the narcotic action of excessive CO_2. (2) Inhalation of 100% *oxygen*. This will indicate the vital rôle of the chemoreceptors, since respiratory activity will be sharply depressed or may cease altogether, and blood pressure will fall.

These two procedures will indicate to the clinician that the respiratory and circulatory status of his patient is precarious and that a marked degree of narcotic depression exists against which the rugged carotid and aortic chemoreceptors are standing alone.

(*b*) *Clinical Anesthesia.* The same factors are at work in a patient breathing room air and anesthetized with pentothal, evipal, or avertin. Here, too, as anesthesia progresses, there is a shift in the control of respiration and circulation from the medulla to the chemoreceptors.[24] If the anesthetist is not aware of this shift, he may note only the fact that breathing and blood pressure are almost normal and may not appreciate the critical central depression. Failing to realize the significance or even the presence of anoxemia, he may be unprepared for cessation of respiration or sharp decline in arterial blood pressure following the addition of subsequent doses of the narcotic agent.[5,43]

The situation is analogous to that of a patient who has suffered moderate to severe hemorrhage but whose blood pressure remains practically normal as the result of powerful compensatory reflexes. An additional mild to moderate hemorrhage may at this point produce shock, because compensatory factors are already functioning maximally.

Cyclopropane would produce the same results as pentothal if it were administered with air instead of with high percentages of oxygen. Cyclopropane depresses respiration profoundly only when a chemoreceptor reflex drive is prevented by the inhalation of high oxygen concentrations. Likewise, if pentothal, avertin or evipal were accompanied by inhalations of 100% oxygen, the increased tension of oxygen in the arterial blood would prevent chemoreceptor activity from obscuring the true state of central depression. In this way the full narcotic depressant action would be continually evident and unexpected disasters would be diminished. Since (in the experience of certain Army groups) deaths following pentothal sodium intravenously are 6 to 7 times more frequent than those following other anesthetics,[10] it appears that this knowledge is not generally appreciated.

All narcotics, however, do not lead to anoxemia. Following the administration of ethyl ether, vinethene, chloroform and ethyl chloride, the minute volume of breathing may not be depressed or may even be increased. All of these substances depress medullary centers directly but fail to produce depressed breathing and arterial anoxemia because of the presence of a variety of specific stimulant actions. If these agents are

administered together with a high concentration of oxygen, no reflex chemoreceptor drive can be expected. However, these drugs are irritant in varying degrees to the respiratory mucosa, and may set up reflex drives over the vagus nerves.[54] There is, furthermore, evidence that ether, at least, may initiate afferent impulses in muscles.[19] Finally, Heinbecker[28] and Adrian[1] feel that ether may even have some direct stimulant action in the central nervous system. Whatever the ultimate site of such stimulation, the fact remains that anoxemia does not commonly accompany the administration of these anesthetics (unless respiratory obstruction of some nature occurs), and increased chemoreceptor activity is therefore not a factor.

It is thus apparent that in anesthesia the chemoreceptors may be of the utmost significance or may play no rôle at all. When arterial anoxemia *does* exist together with narcosis, impulses from the carotid and aortic bodies contribute a great deal towards the maintenance of body function, more perhaps than in any other clinical condition.

2. *Anoxia Associated With Inhalation of Gases With a Low Oxygen Tension.* This is exemplified by an individual breathing low oxygen mixtures at sea level, or by an aviator breathing air at high altitudes. The importance of the chemoreceptors increases progressively with the degree of anoxia. Thus, at an oxygen concentration of 18% in the inspired air (corresponding to an altitude of 3900 feet), practically no evidence of carotid or aortic body activity can be adduced. Most individuals show no increase in respiratory minute volume until a concentration of 14 to 16% oxygen is reached (6900 to 11,000 feet). A few subjects do not even respond to inhalation of 10% oxygen (18,000 feet), although at this level most men increase their respiration by 25 to 35%.[25] As the severity of the anoxia increases, the respiratory and circulatory responses may become quite marked: Horvath *et al.*[34] reported 1 individual whose respiratory minute volume rose to 65 liters during the inhalation of a 4.2% oxygen mixture. (Even at these low oxygen concentrations, widespread individual variation was noted, ranging from 8 to 65 liters per minute).

At least three major factors are concerned in the response to anoxia. Only one of these, the chemoreceptor reflex, is stimulatory to the medullary centers; the other two decrease central reactivity. Of the factors tending to depress the centers, one is a direct action by the anoxia *per se*. The other is an indirect effect of anoxia: When the chemoreceptor response has produced a vigorous hyperpnea, CO_2 is "blown off" and so arterial CO_2 tension is lowered. This leads to decreased function of the medullary centers and so tends to limit the full magnitude of the stimulant phase of anoxia. It also leads to a shifting of respiratory control from the medullary centers to the chemoreceptors, as in narcotic poisoning.

Severe anoxia produces marked stimulant effects (reflexly), but it produces correspondingly great direct central depression and marked decrease in arterial CO_2 tension. It is for this reason that respiratory failure and circulatory collapse may occur when 100% O_2 is inhaled by men who had been breathing very low oxygen mixtures. This response has been termed "oxygen apnea" or "oxygen blackout."[39,42,55,57] The sudden withdrawal of the stimulant factor (chemoreceptor reflexes) by the abrupt rise in arterial oxygen tension reveals the presence of the other two factors (direct and indirect depression of the medullary centers). Respiratory and circulatory depression continue until the arterial CO_2 tension rises and/or until the central effects of anoxia have been overcome.

Mild anoxia produces only slight stimulant effects (reflexly) and, unless very prolonged, does not produce significant depression (centrally). Consequently, administration of 100% oxygen to individuals only mildly anoxic is rarely followed by any dramatic change. Even subjects breathing 10% oxygen for short periods of time show only temporary depression of breathing when shifted to high oxygen concentrations. Minute volume of respiration does fall below normal but only for 60 to 90 seconds tending to level off promptly at a figure close to normal.[25]

It should be emphasized that moderate anoxemia of long duration produces a physiologic state that is closely related to that caused by severe anoxia lasting for shorter periods. It has been demonstrated by Barach[3] that in patients with chronic anoxia (cardiac decompensation, pulmonary fibrosis, chronic bronchitis) the administration of high oxygen mixtures might be followed by a "state of stupor, with irrationality when aroused, lasting for 1 to 5 days." These patients seem to have made some adaptation to their anoxic states (the nature of which remains obscure, although it may be related to a chemoreceptor drive to the cerebral cortex or to a compensatory cerebral vasodilation). In any event, the use of high oxygen concentrations leads to deterioration of mental function, and treatment should begin with 30 to 40% oxygen. These patients, interestingly enough, do not develop oxygen apnea when given 100% oxygen, probably because of vagal respiratory stimulant reflexes arising in the diseased lungs.

3. *Anoxia Associated With Pathologic Changes in the Lungs.* These states are even more involved than those previously discussed. In addition to carotid and aortic body reflexes aroused by oxygen deficit, and the central depression outlined above, other factors must be mentioned.[15,40,52] Most important of these are the Hering-Breuer or vagal lung reflexes activated by unusual distention or collapse of the pulmonary alveoli. These reflexes play a large part in the production of various clinical dyspneas, particularly in asthma, emphysema, pulmonary congestion, and edema. They are initiated by local changes in the lungs and tend to stimulate respiration regardless of the presence or absence of anoxia. Other causes for respiratory stimulation may be sought in the presence of fever (see page 691) or acidosis (see page 690), both of which are accompanied by increase in minute volume of breathing. Finally, in certain pulmonary conditions there may be an elevated CO_2 tension, *e. g.*, emphysema.

Of these five or six mechanisms, which together are responsible for the increased breathing associated with pulmonary disease, only one, the chemoreceptor drive initiated by anoxia, will be affected by oxygen therapy. Since this reflex plays a relatively minor rôle in the cause of clinical hyperpneas,[15,52] removal of this drive may not be followed by any clinically detectable diminution in respiratory effort. The clinician is thus faced with the paradox of an anoxic, hyperpneic patient, in whom the correction of the anoxia leaves the hyperpnea seemingly unchanged.

This may be explained on the following basis: The hyperpnea caused by the degree of anoxia commonly seen clinically is not marked. The inhalation of 10% oxygen causes a 25 to 35% increase in minute volume, and reduces arterial oxygen saturation to 70 to 80%. Since the arterial oxygen saturation of patients with cardiorespiratory disease does not as a rule fall below 70%, it is evident that the degree of anoxia seen in these disorders produces only small increases in respiratory minute volume (rarely sufficient to cause a subjective sensation of dyspnea). Removal

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of this anoxic factor leaves other powerful respiratory stimulant actions unaffected, and leads one to conclude that the chemoreceptors are not of prime importance in the production of clinical dyspnea.

Because of the many complicating factors that may and usually do enter into the clinical picture of anoxia, the response of the anoxic patient to oxygen therapy may appear to be unpredictable and capricious. It is hoped that a clear understanding of the mechanisms discussed above will enable the clinician to evaluate the physiologic state of his patient. In this regard, two points deserve special emphasis: (1) The absence of circulatory or respiratory changes following inhalation of oxygen does not mean that oxygen is without value. Oxygen inhalation often abolishes cyanosis without reducing dyspnea. (2) The occurrence of respiratory or circulatory depression following oxygen administration does not call for an abandonment of this type of therapy. However, one must be prepared for such a response and must carry on respiratory gas exchange artificially for a while, if necessary. Anoxemia is a serious threat to central nervous system and myocardial function. The longer oxygen lack exists, the more likelihood there is of permanent cell damage.

Increased Acidity. It has been thought for many years that the regulation of normal and abnormal respiration is accomplished by the pH of the arterial blood acting centrally or by the pH in the cells of the respiratory center itself. Two things have occurred in the last few years which appear to invalidate this hypothesis: one was the recent demonstration that respiration is not nearly so sensitive to changes in pH* as formerly believed[17,44] and the other was the discovery that the carotid bodies (and presumably the aortic bodies as well) *do* respond to changes in arterial pH and apparently are capable of producing a response equal to that of the entire organism. It should be pointed out that the evidence on this score is far from satisfactory, for the simple reason that it is a difficult matter to increase blood acidity without producing simultaneously a change in arterial pCO_2 because of the chemical reaction between acid and bicarbonate. For this reason, it is difficult to evaluate those experiments in which either the brain[33] or the carotid bodies[53] have been perfused with acidified blood, and it has been found necessary to perfuse the chemoreceptors with saline solutions (without $NaHCO_3$) in order to determine quantitatively the uncomplicated effects of acidity upon them. Schmidt, Comroe and Dripps[53] performed such experiments in 1939, but since saline perfusions of an organ are admittedly abnormal, the results obtained probably do not indicate the true sensitivity of the chemoreceptors. Nevertheless, it was shown that respiration and blood pressure were increased by decrease in pH of as little as 0.1 unit and were augmented markedly (200 to 300%) by a decrease in pH of 0.4 unit.

The degree of sensitivity of the respiratory center or of the chemoreceptors of man to changes in pH is still uncertain, though there is reason to believe that the response is slight with small changes in pH, yet may be marked with definite uncompensated acidosis. Nielsen[44] found an increase of only 0.7 L. per minute with a pH decrease of 0.08 unit, and Dennig *et al.*[23] observed an increase of 3.1 L. with a drop of 0.2 pH unit in man.

The conditions in which uncompensated acidosis most frequently occurs

* The recent experiments of Banus *et al.*[2] purporting to show an extreme sensitivity of the respiratory center to pH changes, cannot be accepted because of the fact that not a single control experiment was performed. Since animals anesthetized with barbital tend gradually to come out of anesthesia, increased respiration is to be expected over a period of time.

are diabetic coma, terminal nephritis, dehydration or starvation, ammonium chloride administration and severe muscular exercise; arterial pH may be lowered just perceptibly or may fall as low as pH 6.98.[21] In view of the great interest of both respiratory physiologists and clinicians in acidosis, it is amazing to see how few simultaneous measurements of arterial pH and respiratory minute volume have been made in patients. The Kussmaul breathing of acidosis has been frequently mentioned but rarely measured. In cases of severe diabetic or nephritic acidosis with definite fall in arterial pH, respiratory minute volumes of 10.6,[40] 11.4[35] or as high as 55 L. per minute[41] have been recorded. It is possible that this response may be attributable wholly or largely to chemoreceptor activity (though occasionally complicating factors such as fever, pneumonia, or even circulatory failure may contribute to the hyperpnea). In this regard a very interesting observation is that of Schecter,[46] who reported circulatory collapse following intravenous administration of alkali to patients with severe diabetic acidosis. In light of present knowledge, this may be explained by postulating a depressant action of uncompensated acidosis upon the vasomotor centers counteracted only by reflex stimulation due to the action of decreased pH upon the chemoreceptors; when the reflex stimulation is suddenly withdrawn, due to rapid infusion of $NaHCO_3$, the depressed centers are unable to function properly and circulatory failure occurs. Viewed in this way, this accident becomes wholly analogous to the "oxygen apnea" produced by oxygen administration in an anoxic individual (see page 688).

Clinically, therefore the possibility exists that the hyperpnea seen in various types of acidosis may be caused by carotid and aortic body reflexes. Further experiments along this line are indicated.

Fever. It has been demonstrated clearly in dogs by Bernthal and Weeks[7] and by Schmidt, Comroe and Dripps[53] that warming the chemoreceptors 3° to 4° C. above normal body temperature results in a 33 to 70% increase in respiratory minute volume; cooling the carotid bodies depresses respiration and blood pressure. This respiratory stimulation is characterized by an increase in both rate and depth of respiration and hence is not related to the shallow panting respiration commonly seen in dogs in hot weather. Increased body temperature might also increase respiration in other ways: (*a*) by stimulation of cerebral centers cephalad to the medulla, (*b*) by increase in metabolism of the medullary respiratory centers, and (*c*) by decrease in blood pH resulting from the effect of heat upon blood as a physicochemical system.[58]

It is unlikely that the portion of the hyperpnea of fever (acute infections, severe muscular exercise, and so on) contributed by the carotid and aortic bodies will ever be determined in man. It seems possible, however, that as in anoxic states, the rôle of the chemoreceptors in febrile conditions may become more important during narcosis. This is of particular interest to an anesthetist who commonly uses the to-and-fro carbon dioxide absorbing closed system methods for administering inhalation anesthetics. The temperature of the inspired air rises as anesthesia progresses due to conservation of body heat (by the closed system) and to the generation of heat by the chemical reaction of soda lime with CO_2. Consequently, rise in body temperature may occur in the anesthetized patient and may contribute, by chemoreceptor reflexes, to the respiratory and circulatory stimulation often observed.

Increased Carbon Dioxide Tension. It has been well established[26,53] that an increase in CO_2 tension acting upon the chemoreceptors will re-

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flexly increase respiration, pulse rate, blood pressure and vasomotor tone. It is equally well established that this response requires an increase in CO_2 tension far in excess of that required to stimulate the medullary centers. Therefore small to moderate increases in arterial CO_2 tension will stimulate respiration and circulation without the aid of carotid or aortic body activity.

One might assume that the chemoreceptors, being highly resistant structures, would respond to an elevated arterial CO_2 tension (as well as to anoxemia) after the medullary centers had become so depressed by narcosis or anoxia as to be unable to respond to CO_2. However, the response of the chemoreceptors to increased CO_2 is not only relatively weak, but appears also to be depressed by the same conditions that depress the central CO_2 response. In this respect, the response of the chemoreceptors to increased CO_2 differs from that to anoxia. Consequently high concentrations of CO_2 do not stimulate reflexly in a subject with depressed centers, and may actually further depress these centers through a direct narcotic action.

From the clinical standpoint, it is apparent that the carotid and aortic bodies are relatively unimportant as far as response to CO_2 is concerned. The threshold of the chemoreceptors is too high and, as CO_2 tension increases in the blood, it is a central rather than a peripheral stimulation which is of major concern.

Action of Drugs. The first indication that chemoreceptor reflexes were concerned in drug actions was the demonstration by Heymans in 1927 that nicotine could stimulate respiration through reflexes arising in the aorta. Since then a number of other drugs have been found to act on both the carotid and aortic bodies.* Cyanides, sulfides, lobeline, potassium salts, a variety of choline derivatives, and Nikethamide can all be shown to stimulate these end-organs. As far as the mechanism of action is concerned, some facts are evident. The action of cyanide and sulfide is essentially the same as anoxia, these drugs producing oxygen lack through paralysis of cellular respiratory enzymes. Potassium apparently is stimulant to all nerve cells and endings in the body, and its effect on chemoreceptors is one manifestation of this property. Nicotine, lobeline and those choline derivatives with a nicotine-like action, stimulate ganglion cells throughout the body and may stimulate similar cells believed to occur in the carotid and aortic bodies, though recent cytologic studies of Hollinshead indicate that these "ganglion cells" are not nerve tissue but specific "sensory cells."[32]

Certain of the drugs acting upon the chemoreceptors are important to the clinician:

1. Several of these drugs have been used to test arm-to-carotid circulation time. The characteristic response of the carotid and aortic bodies to the intravascular injection of stimulant drugs is a gasp. This gasp can readily be detected clinically, and forms the basis for an objective test of circulatory velocity.[11,38] The drugs (cyanide or lobeline) are injected intravenously, and the onset of the respiratory response noted.

* We must stress again the difference between carotid sinus-aortic arch pressure receptors and the carotid and aortic body chemoreceptors. It is extremely unlikely that drugs act on pressure receptors. Their very nature as stretch organs indicates a response to distention rather than to pharmacologic agents. Despite this, two inaccuracies are current in the clinical literature: (1) drug action on the carotid sinus and aortic arch mechanisms are described on the basis of very sketchy evidence, and (2) authors fail to indicate whether a particular drug action discussed is attributable to the chemo- or pressoreceptors.

The time necessary to transport the drugs from the site of administration to the chemoreceptors is a measure of the speed of the circulation. Recent evidence indicates that papaverine, another substance used to measure circulation time, also produces its characteristic respiratory response reflexly through an action on the chemoreceptors.[25]

2. Lobeline has been used in an effort to stimulate breathing in newborn infants who are slow to assume normal respiratory activity immediately after birth. The action of the drug, as far as respiratory stimulation is concerned, is upon the chemoreceptors. Because of this, whatever stimulation occurs will be brief and is of value only as a sudden "kick" to a sluggish respiratory center. However, its ability to produce a few gasps may aid materially in expanding atelectatic lungs.[60] Prolonged stimulation from a single dose of lobeline cannot be expected, and repeated doses should not be given because of the danger of producing depression.

3. Cyanide poisoning: Hydrocyanic or prussic acid blocks oxygen uptake in cells through paralysis of intracellular oxidation. The hemoglobin may be saturated with oxygen; oxygen tension may be normal in the arterial blood, yet tissue death occurs from cellular (histotoxic) anoxia. Initial respiratory and circulatory stimulation are clinical characteristics of cyanide toxicity, and this response is due to a cyanide action of the chemoreceptors. It should be pointed out that only very small doses of cyanide are utilized in the circulation test described above, and that only a transient cellular anoxia is produced in the chemoreceptors, or elsewhere, since cyanide is very rapidly detoxified in the body.

4. The statement has been made that Heymans believed atropine to be depressant to the carotid reflexes. This is an error in interpretation, and has resulted in some erroneous clinical beliefs. Actually, Heymans stated that atropine blocked the cardiac vagus and so prevented the cardiac slowing which otherwise followed stimulation of the carotid *sinus*. In 1941, Burstein[12] concluded that atropine and scopolamine depressed chemoreceptor response and that the use of these drugs, so commonly employed in the preoperative period was hazardous. Phelps also regarded atropine as a depressant to the chemoreceptors.[45] Evidence that atropine has no action on the chemoreceptors was provided by Schmidt and Comroe.[18] Burstein's results are not questioned, but they can be explained on an entirely different basis. Atropine should therefore not be regarded as depressant to the carotid and aortic bodies.

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BOOK REVIEWS AND NOTICES

VIRUS DISEASES IN MAN, ANIMAL AND PLANT. A Survey and Reports Covering the Major Research Work Done During the Last Decade. By GUSTAV SEIFFERT. English translation by MARION LEE TAYLOR, PH.D. Pp. 332; 7 figs.; 7 tables. Published upon recommendation of the National Research Council. New York: Philosophical Library, 1944. Price, $5.00.

THIS book is a fairly complete review of the more important works in the vast literature on virus research up to about the year 1937. The aim of the author is to present an introduction into the virus field for those who wish to study it quite thoroughly. References are made to reviews or important publications on each virus and virus disease covered in the text.

The text embodies 5 divisions: (1) a general concept of viruses and virus diseases; (2) specific virus diseases (some covered completely, others merely mentioned); (3) virus-like organisms, including the Rickettsia, Bartonella, Pleuropneumonia and others; (4) filterable types of bacteria; and (5) methods of virus investigation. (This is recognized as incomplete by the author.)

The rapid advances in virus research since 1937 seems to call for a more recent review text of this type to supersede or supplement this text, although many of the fundamentals of knowledge on virus diseases were uncovered before this publication. In some parts the text is awkward and not clearly presented, probably because of a too literal translation by someone not too familiar with virus or medical terminology. The references to other publications were not without error. While not complete, however, this review text does give the student of viruses (vira) an insight into the important advances in his field. F. E.

THE DIET THERAPY OF DISEASE. A Handbook of Practical Nutrition. By LOUIS PELNER, M.D., Assistant Attending Physician, Long Island Hospital, Greenpoint Hispital, and Brooklyn Cancer Institute; Gastroscopist, Beth Moses Hospital; Lecturer, Post-Graduate Course in Gastroenterology, under the charge of Dr. S. A. Seley. Pp. 143. New York: Personal Diet Service 1944. Price, $3.75.

"THE Diet Therapy of Disease" is, as the author states in his Preface, a somewhat ambitious title for this book. It is rather a compilation of some of the diets that are used by the Personal Diet Service of which the author is editor. The book contains 44 diets for some 25 different conditions, each being preceded by a short résumé of the physiology of the disease. The concise form of the diets and the ease with which they can be understood may be of some value to the busy practitioner, but the preliminary discussions are confused, contradictory, and filled with grammatical errors. Not all of this can be blamed on poor type-setting or careless proofreading; for instance, the author speaks (p. 16) of certain essential fatty acids "such as arachidonic and perhaps linoleic and linoleic acids" when he obviously intends one of them to be linolenic. It seems to the Reviewer that little excuse can be offered for the publication of such a book. E. B.

THE MICROSCOPE. By R. M. ALLEN. Third printing. Pp. 286; 17 plates; 82 figs. New York: D. Van Nostrand, 1944. Price, $3.00.

THE medical sciences owe a tremendous debt to the microscope. Many of their advances could not have been made without it. This book has been written in such a way that the theory and manipulation in microscopy might be understood by even those with little technical training. The author has

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not intended the text to be an encyclopedia on microscopy and so treats only the essential details on each subject.

There are chapters on the historical background, optical principles, descriptions and analyses of the types of modern instruments, methods of illumination, methods for testing microscope objectives, how to get the most out of a microscope and preparation of material for microscopic examination. One of the most instructive is the chapter on Getting the Most Out of the Microscope. The author presents hints for both the beginner and expert on how to increase the potentialities of his microscope.

Here is a book that would be of great value to everyone who uses a microscope in his work. It could act as a guide in the choice of a new instrument as well as in testing the value of his laboratory equipment. By following the principles suggested by the author, one could easily increase the value of his standard equipment and his ability in its use. A text of this type could have tremendous value in teaching institutions where the fundamentals of microscopy should be implanted correctly. This book should be had in all teaching and research laboratories as a guide in the technique of microscopy. F. E.

PHOTO-MICROGRAPHY. By R. M. ALLEN. Pp. 265; 50 plates; 175 figs. New York: D. Van Nostrand, 1941. Price, $5.50.

EVERYONE in science who uses a microscope in his work has at one time or other come upon some microörganism, some field in a histologic section, or pathologic lesion, a chemical crystal or other microscopic structure which he would like to include in his permanent records. In answer to his needs the author of "The Microscope" has written an authoritative text which explains all the fundamentals in photography as taken through a microscope. It is not written in complicated terminology but in a way that all scientific workers can understand and apply the methods explained.

There are chapters on fundamentals, modern equipment, homemade equipment, technique of photomicrography, special applications ranging from metallography through to the electron microscope, microphotography (microfilm), photographic processes, materials and equipment, as well as a series of 50 representative photomicrographs showing what can be done in many fields by applying methods as described in the text.

This text should be of great use for all laboratories using photography in their microscopic work. Especially important for most laboratories are the sections on "Homemade Equipment" and "The Technique of Photomicrography." It is not every laboratory that can afford the complete equipment or a full-time photographer trained in such methods. Here is a book giving the methods and techniques that one can use to complete a microphotographic set-up for his own laboratory with the minimum time and effort as well as to train himself to become highly proficient in photomicrography. This book cannot be too highly recommended. F. E.

A BIO-BIBLIOGRAPHY OF ANDREAS VESALIUS. By HARVEY CUSHING, M.D.; Preface by JOHN F. FULTON, M.D. Publication No. 6—Historical Library of Yale Medical Library. Pp. 229; 89 figs. New York: Schuman, 1943. Price, $15.00.

THE HARVEY CUSHING COLLECTION OF BOOKS AND MANUSCRIPTS. Publication No. 1—Historical Library of Yale Medical Library; Preface by JOHN F. FULTON, M.D. Pp. 207. New York: Schuman, 1943. Price, $8.50.

LOVERS of beautiful books and devotees of the history of medicine had good reason to mourn when Paul Hoeber passed from the scene. Now, however, they have equally good grounds for hope that a similar rôle may be filled by Schuman's of New York. Certainly these two Cushing books—both publications of the Historical Library of the Yale Medical Library—set a standard of distinction and excellence that leaves little to be desired.

The Bio-bibliography of Andreas Vesalius—the more important of the two—

is the fruition of Dr. Cushing's many years of study of the man and his works. In the Preface, Dr. Fulton dates this interest from 1898 or earlier; incidentally I recall, some years after that, Cushing mentioning that he hoped he might some day produce an English translation of the Fabrica. This was not to be, and even the Bio-bibliography, which he hoped to have published for the quadricentennial of the Fabrica, was apparently far from finished at his death in 1939. We, and the book itself, owe much therefore, to Drs. Fulton, Francis and Castiglioni, Mrs. Peters and others for completing, revising and editing the text. In spite of these difficult times, they have attained Dr. Cushing's goal of publication in 1943, the Vesalius Anniversary year.

We are given a good background of preliminary pages to prepare us for the Bio-bibliography proper. Following a sensitive and appreciative Preface by Fulton, the author offers a characteristically lively apologia—would that it had been longer! Next come a few pages to "place" Vesalius (but why call them Bio-bibliography?); more on Vesalius and Calcar, and Cardan's Horoscope of Vesalius, and then the main text. This is divided into chapters, one for each of Vesalius' 7 works; one (by Castiglioni) on Fallopius and Vesalius, and one on Vesaliana compiled by Mrs. Peters. Valuable to all who are interested in Vesalius—and what lover of medical history is not?—this book becomes an absolute necessity for students of that great figure.

THE second volume, a short title catalogue of the Harvey Cushing Collection of Books and Manuscripts, now in the Medical History branch of the Yale Library, was made possible by a bequest in Dr. Cushing's will. When the Catalogue is supplemented, as is the intention, by similar catalogues of the Klebs and Fulton collections in the same library, a tool for students of medical history both in and outside of New Haven will have been created that will be equal to or perhaps even surpassing the celebrated Bibliotheca Osleriana. The items are divided into 5 classes: Manuscripts, Orientalia, Incunabula, General Works (comprising the great bulk of the contents), and Cushing Memorabilia. The job has been carefully done by trained librarians; unavoidable inconsistencies are recognized and avoidable ones avoided. Frequent citations to this or that reference work are given for those seeking fuller details, in the case of items published before 1800. Thus is one more item added to Yale's beautiful Medical History Library on the road toward fulfilling its destiny as a focus for productive scholarship. E. K.

FUNDAMENTALS OF PSYCHIATRY. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department, School of Medicine, Univ. of Penna.; Psychiatrist to the Pennsylvania Hospital; Attending Psychiatrist, Philadelphia General Hospital; Consultant to the Bureau of Medicine and Surgery, U.S.N.; Consultant to the Secretary of War, A.A.F. Second ed. Pp. 219; 15 figs. Philadelphia, London, Montreal: J. B. Lippincott, 1944. Price, $3.00.

THE 2nd edition of this little book needs no revision. It is a concise and well-written account of the psychosis and psychoneuroses as they occur in peace and war. The chapter on classification should help all those not well versed in the nomenclature of mental illness. A glossary of terms, uniquely printed on the end papers, is most useful. The value of the book is in inverse proportion to its pocket size. H. S.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut. Colonel, M.R.C., U.S.A.; Member of the Com. on Nomenclature and Classification of Diseases of the American Medical Association; Editor of "American Pocket Medical Dictionary." With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia Twentieth ed. Pp. 1668; 885 illus.; 240 portraits. Philadelphia and London: W. B. Saunders, 1944. Price, plain—$7.00; Thumb-indexed—$7.50.

PERUSAL of successive editions of our leading medical dictionaries invariably produces in this reader the same two responses: (1) what accurate, up-to-date,

inclusive and conveniently helpful books they are; (2) how difficult it is to make a choice between them. This latest edition of "Dorland" contains hundreds of new words not to be found in any other similar work, but the same could probably be said of "Stedman," if a new edition should happen to come out in the next year or two. It is also noteworthy that the terminology in this edition conforms to that of "The Standard Nomenclature of Diseases and Operations." "Dorland's" specializes on useful lengthy groupings of many items, often eponymic, in such categories as Diets (2 columns), Diseases (13 columns), Methods (14 columns), Syndromes (10 columns), and so on. A list of these and of Tables used occupies a full page just after the Preface. Naturally, many of these words included have never been of any importance and may be quite obsolete, but these may be just the ones that are hardest to trace elsewhere; and it should be remembered that a dictionary exists primarily to inform the seeker and not to educate.

Twenty editions in 45 years go far toward demonstrating not only the need for such books but also the rapid progress of a science that requires such frequent revisions, and the value of such a nest egg for a medical publisher!

E. K.

VASCULAR RESPONSES IN THE EXTREMITIES OF MAN in Health and Disease. By DAVID I. ABRAMSON, M.D., F.A.C.P. Pp. 412; 59 figs.; 4 tables. Chicago Univ. of Chicago Press, 1944. Price, $5.00.

THIS is a splendid contribution to a rapidly growing field. The author has used a dynamic approach which permits critical judgment on therapeutic measures from the functional standpoint. Various forms of treatment can now be evaluated on the basis of sound pharmacologic and physiologic grounds rather than on the more empirical and less scientific clinical approach. The book should prove a great stimulus to investigators of normal and abnormal circulation. Experimental methods are outlined critically, and gathered together for the first time.

For the clinician, there is perhaps insufficient detail in the sections designated "clinical application." In many of these, drugs are considered without dosage schedules (*e. g.*, the use of papaverine as a vasodilator) in the case of hypertonic saline solution the amount to be employed is not given, etc. A more complete outline of the various therapeutic measures suggested would be helpful.

R. D.

NEW BOOKS

Malaria: Its Diagnosis, Treatment and Prophylaxis. By WILLIAM N. BISPHAM, Colonel, U. S. Army, Retired. Pp. 197. Baltimore: Williams & Wilkins, 1944. Price, $3.50.

Plaster of Paris Technic. By EDWIN O. GECKELER, M.D., Associate Professor of Orthopædic Surgery, and Chief of the Fracture Service, Hahnemann Med. Coll. and Hosp., Philadelphia; Fellow of the Am. Coll. of Surgeons, Fellow of the Am. Acad. of Orthopædic Surgeons, Fellow of the Am. Assn. for the Surgery of Trauma, Diplomate of the Am. Board of Orthopædic Surgery. Pp. 220; 208 figs. Baltimore: Williams & Wilkins, 1944. Price, $3.00.

The Urinary Tract. A Handbook of Roentgen Diagnosis. By H. DABNEY KERR, M.D., Professor of Radiology, State Univ. of Iowa Coll. of Med., and CARL L. GILLIES, M.D., Associate Professor of Radiology, State Univ. of Iowa Coll. of Med. Pp. 320; numerous figs. Chicago: Year Book Publishers, 1944. Price, $5.50.

Poisonous Plants of Hawaii. By HARRY L. ARNOLD, M.D., Honolulu. Pp. 71; 24 plates. Honolulu, Hawaii: Tongg Publishing Co., 1944.

Hipertension Arterial Nefrogena. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCIOLO, LUIS F. LELOIR, JUAN M. MUNOZ, and ALBERTO C. TAQUINI. Instituto de Fisiologia de la Facultad de Ciencias Medicas de Buenos Aires; Instituto de cardiologia Fundacion V. F. Grego. Pp. 462; 93 figs. Buenos Aires: Liberia y Editorial "El Alteneo," 1943.

Cataract and Anomalies of the Lens. Growth, Structure, Composition, Metabolism, Disorders, and Treatment of the Crystalline Lens. By JOHN G. BELLOWS, M.D., PH.D., Assistant Professor of Ophthalmology, Northwestern Univ. Med. School, Chicago. Pp. 624; 208 figs.; 4 color plates. St. Louis: Mosby, 1944. Price, $12.00.

Advances in Protein Chemistry. Edited by M. L. ANSON, Continental Foods. Hoboken; JOHN T. EDSALL, Harvard Med. School, Boston; and 9 Contributors. Vol. 1. Pp. 341; numerous figs and tables. New York: Academic Press, 1944. Price, $5.50.

Vitamins and Hormones. Advances in Research and Applications. Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Inst. of Technology, Cambridge, Mass.; KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard Univ., Cambridge, Mass. Vol. 2. Pp. 514; numerous figs. and tables. New York: Academic Press, 1944. Price, $6.80.

A Textbook of Pathology. Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease. By ROBERT ALLAN MOORE, Edward Mallinckrodt Professor of Pathology, Washington Univ. School of Med., St. Louis. Pp. 1338; 513 figs.; 34 in color. Philadelphia and London, Saunders, 1944. Price, $10.00.

Our American Babies. The Art of Baby Care. By DOROTHY V. WHIPPLE, M.D. Introduction by C. ANDERSON ALDRICH, M.D., Chief of Staff, The Children's Memorial Hosp., Chicago. Pp. 367; numerous figs. and tables. New York: M. Barrows, 1944. Price, $2.50.

Women and Men. By AMRAM SCHEINFELD, Author of "You and Heredity." Pp. 453. Illustrations by the Author. New York: Harcourt, Brace, 1944. Price, $3.50.

An intelligent, and apparently accurate presentation for the laity.

The Medical Clinics of North America. Symposium on Specific Methods of Treatment. The Boston Number. 22 Contributors. Pp. 1292; 96 figs. Philadelphia and London: Saunders, 1944.

Surgery of the Hand. By STERLING BUNNELL, M.D., Honorary Member of Am. Acad. of Orthopedic Surgeons, Member of Am. Assn. of Plastic Surgeons and of Am. Soc. of Plastic and Reconstructive Surgery, Licentiate of Am. Board of General Surgery and Plastic Surgery. Pp. 734; 597 illus. Philadelphia, Lippincott, 1944. Price, $12.00.

Mitosis. The Movements of Chromosomes in Cell Division. By FRANZ SCHRADER, Professor of Zoölogy, Columbia Univ. Pp. 110; 15 figs. New York: Columbia Univ. Press, 1944. Price, $2.00.

We are unimpressed. D. C.

NEW EDITIONS

Diseases of the Digestive System. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Professor of Medicine, Univ. of Illinois Med. School (Rush); Attending Physician, Michael Reese Hosp.; Consulting Physician, Cook County Hosp.; Consultant in Medicine to the Inst. of Psychoanalysis, Chicago. Second Ed. Pp. 932; 182 illus. Philadelphia: Lea & Febiger, 1944. Price, $11.00.

The Radiology of Bones and Joints. By JAMES F. BRAILSFORD, M.D., PH.D., F.R.C.P., F.I.C.S. Third Ed. Pp. 440; 404 illus. Baltimore: Williams & Wilkins., 1944. Price, $12.00.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (BERLIN), Director of the Medical Division, Bikur Cholim Hosp., Jerusalem; Late Extraordinary Professor of Medicine in the Univ. of Berlin and Director of the Medical Division of the Krankenhaus Am Urban in Berlin. Translated by CARL PRAUSNITZ GILES, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Late Honorary Research Fellow, Victoria Univ. of Manchester; Late Professor of Hygiene and Bacteriology, Univ. of Breslau. Fourth (second English) Ed. Pp. 496; 178 figs. Baltimore: Williams & Wilkins, 1944. Price, $11.00.

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Recent Advances in Anæsthesia and Analgesia (Including Oxygen Therapy). By C. LANGTON HEWER, M.B., B.S. (LOND.), D.A. (ENG.). Fifth Ed. Pp. 343; 141 figs. Philadelphia: Blakiston, 1944. Price, $5.50.

Principles of Chemistry. An Introductory Textbook of Inorganic, Organic, and Physiological Chemistry for Nurses and Students of Home Economics and Applied Chemistry. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, School of Med., George Washington Univ.; Formerly Instructor in Chemistry, Central School of Nursing, Washington, D. C. Sixth Ed. Pp. 403; 47 figs.; 4 color plates; 15 tables. St. Louis: Mosby, 1944. Price, $2.75.

A Laboratory Guide in Chemistry. By JOSEPH H. ROE, PH.D., Professor of Biochemistry, The School of Med., George Washington Univ., Washington, D. C.: Pp. 191; numerous illus.; 2 color plates. St. Louis: Mosby, 1944. Price, $1.00.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Anatomy, The School of Med., Washington Univ., and Director of Research, The Barnard Free Skin and Cancer Hospital, St. Louis, Mo. Third Ed., thoroughly revised. Pp. 426; 317 figs.; 13 in color. Philadelphia: Lea & Febiger, 1944. Price, $7.00.

Child Care and Training. By MARION L. FAEGRE, Assistant Professor of Parent Education, and JOHN E. ANDERSON, Director, Institute of Child Welfare, Univ. of Minnesota. Sixth Ed., revised. Pp. 314; numerous illus. Minneapolis: Univ. of Minnesota Press, 1943. Price, $2.50.

Atlas of Dental and Oral Pathology. Prepared at the Army Institute of Pathology of the Army Medical Museum Office of the Surgeon-General, Washington, D. C. From Material in the Registry of Dental and Oral Pathology by JAMES B. MANN, Col., Dental Corps, U.S.A., Former Pathologist to the Registry; J. E. ASH, Col., M.C., U.S.A., Curator; JOSEPH L. BERNIER, Major, Dental Corps, U.S.A., Former Pathologist to the Registry. Third Ed. Revised by HENRY M. GOLDMAN, Lt., Dental Corps, Pathologist to the Registry. Pp. 310. Washington: American Registry of Pathology, 1944.

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